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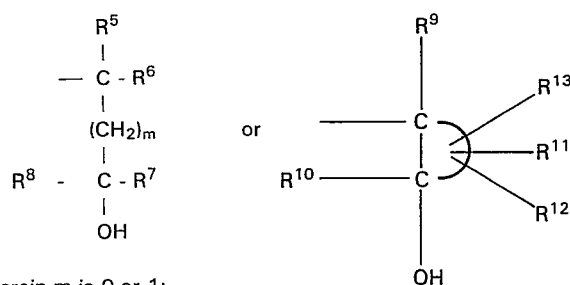
Polycyclic compounds, their preparation and formulations containing them.

The present invention provides a compound of the formula (I):



or a monomethyl or monoethyl ether thereof, the compound of formula (I) including the said ethers containing no more than 29 carbon atoms in total; an ester thereof; a salt thereof; wherein Ar is a 6,6,6,5 tetracyclic aromatic ring system having 15 to 17 ring atoms, the five membered ring containing one heteroatom, optionally substituted by one or two substituents, said substituents containing not more than four carbon atoms in total when taken together and being the same or different and are selected from halogen; cyano; C₁₋₄ alkyl or C₁₋₄ alkoxy, each optionally substituted by hydroxy or C₁₋₂ alkoxy; halogen substituted C₁₋₂ alkyl or C₁₋₂ alkoxy; a group (S(O)_n)R² wherein n is an integer 0, 1 or 2 and R² is C₁₋₂ alkyl optionally substituted by hydroxy or C₁₋₂ alkoxy; or Ar is optionally substituted by a group NR³R⁴ containing not more than 5 carbon atoms wherein R³ and R⁴ are the same or different and each is a C₁₋₃ alkyl group or NR³R⁴ forms a five- or six-membered heterocyclic ring optionally containing one or two additional heteroatoms;

R¹ contains not more than eight carbon atoms and is a group



R⁵ and R⁶ are the same or different and each is hydrogen or C₁₋₅ alkyl optionally substituted by hydroxy;
R⁷ and R⁸ are the same or different and each is hydrogen or C₁₋₃ alkyl;

C-C is a five- or six-membered saturated carbocyclic ring;
R⁹ is hydrogen, methyl or hydroxymethyl;
R¹⁰, R¹¹ and R¹² are the same or different and each is hydrogen or methyl;
R¹³ is hydrogen, methyl, hydroxy or hydroxymethyl.

Also provided are methods for the preparation of the compounds of formula (I), intermediates in their preparations and pharmaceutical formulations containing them.

The compounds of the formula (I) are useful in the treatment of tumours.

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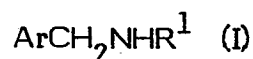
POLYCYCLIC BIOCIDAL COMPOUNDS, THEIR SYNTHESIS
AND INTERMEDIATES THEREFOR,
FORMULATIONS CONTAINING THEM, AND THEIR USE IN MEDICINE

The present invention relates to heteropolycyclic alkanol derivatives which have been found to have biocidal activity. More specifically the invention concerns aminoalkanol derivatives containing a heteropolycyclic ring system, methods for the synthesis thereof, novel intermediates thereof, pharmaceutical formulations thereof and the use thereof as biocidal agents, particularly antitumor agents.

Two analogues of nitracrine (1-nitro-9-((3-dimethylaminopropyl)amino)acridine) containing 2-amino-2-methyl-1,3-propanediol and tris(hydroxymethyl)methylamine groups have been reported to have antitumor activity in some murine screening systems (Arzneim. Forsch./Drug Res. 32II, 1013 (1982)).

We have now discovered a novel class of heteropolycyclic aromatic alkanol derivatives which have biocidal activity.

Accordingly, in a first aspect, the present invention provides a compound of the formula (I)

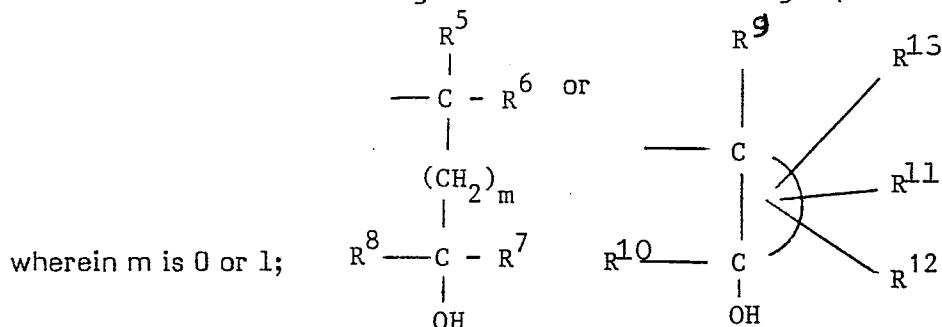


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or a monomethyl or monoethyl ether thereof, the compound of formula (I) including the said ethers containing no more than 29 carbon atoms in total; an ester thereof; a salt thereof;

wherein Ar is a 6,6,6,5 tetracyclic aromatic ring system having 15 to 17 ring atoms, the five membered ring containing one heteroatom, optionally substituted by one or two substituents, said substituents containing not more than four carbon atoms in total when taken together and being the same or different and are selected from halogen; cyano; C_{1-4} alkyl or C_{1-4} alkoxy, each optionally substituted by hydroxy or C_{1-2} alkoxy; halogen substituted C_{1-2} alkyl or C_{1-2} alkoxy; a group $S(O)_n R^2$ wherein n is an integer 0, 1 or 2 and R^2 is C_{1-2} alkyl optionally substituted by hydroxy or C_{1-2} alkoxy; or Ar is optionally substituted by a group $NR^3 R^4$ containing not more than 5 carbon atoms wherein R^3 and R^4 are the same or different and each is a C_{1-3} alkyl group or $NR^3 R^4$ forms a five- or six-membered heterocyclic ring optionally containing one or two additional heteroatoms;

R^1 contains not more than eight carbon atoms and is a group



wherein m is 0 or 1;

R^5 and R^6 are the same or different and each is hydrogen or C_{1-5} alkyl optionally substituted by hydroxy;

R^7 and R^8 are the same or different and each is hydrogen or C_{1-3} alkyl; $-C-C-$ is a five- or six-membered saturated carbocyclic ring;

R^9 is hydrogen, methyl or hydroxymethyl;

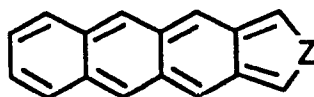
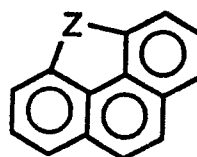
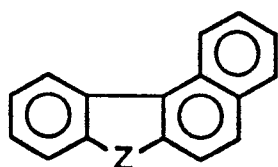
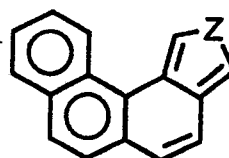
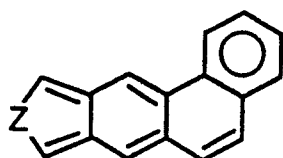
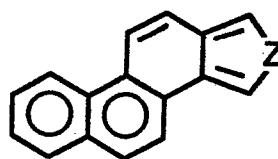
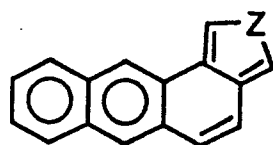
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R^{10} , R^{11} and R^{12} are the same or different and each is hydrogen or methyl;

R^{13} is hydrogen, methyl, hydroxy, or hydroxymethyl;

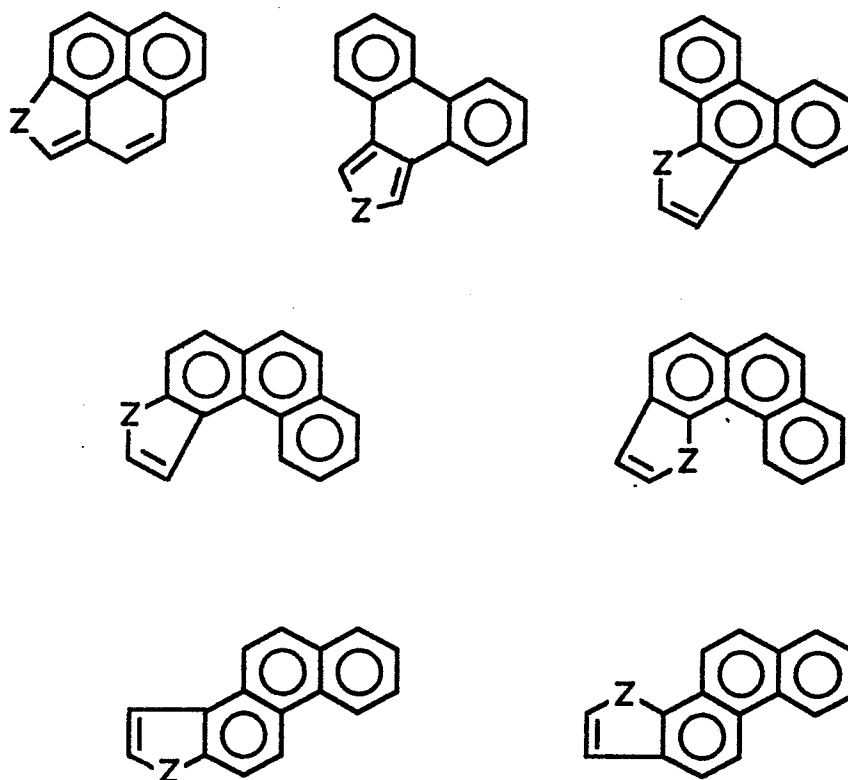
The heteroatom is preferably oxygen, sulphur or nitrogen. When it is nitrogen, this is substituted by hydrogen, methyl or ethyl; preferably by methyl or ethyl.

Aromatic ring systems within the scope of the present invention include:



Z is a heteroatom

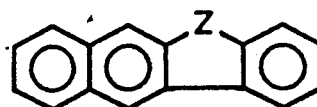
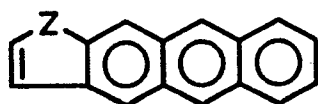
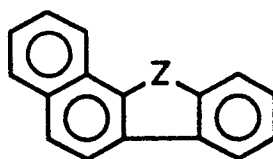
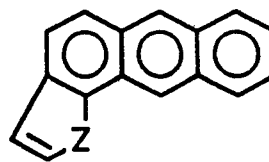
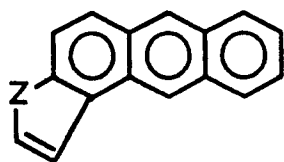
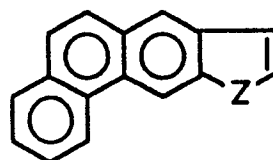
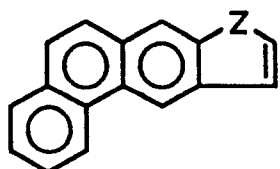
6,6,6,5-Tetracyclic Ring Systems



Z is a heteroatom

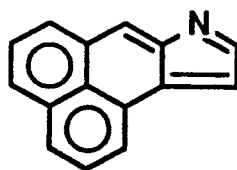
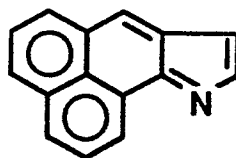
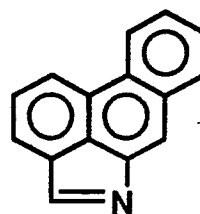
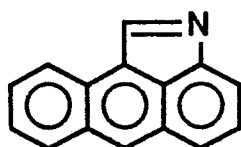
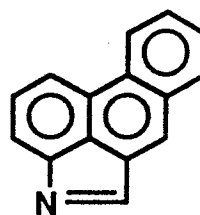
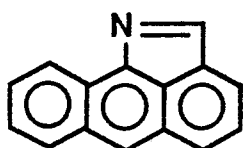
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6,6,6,5-Tetracyclic Ring Systems



Z is a heteroatom

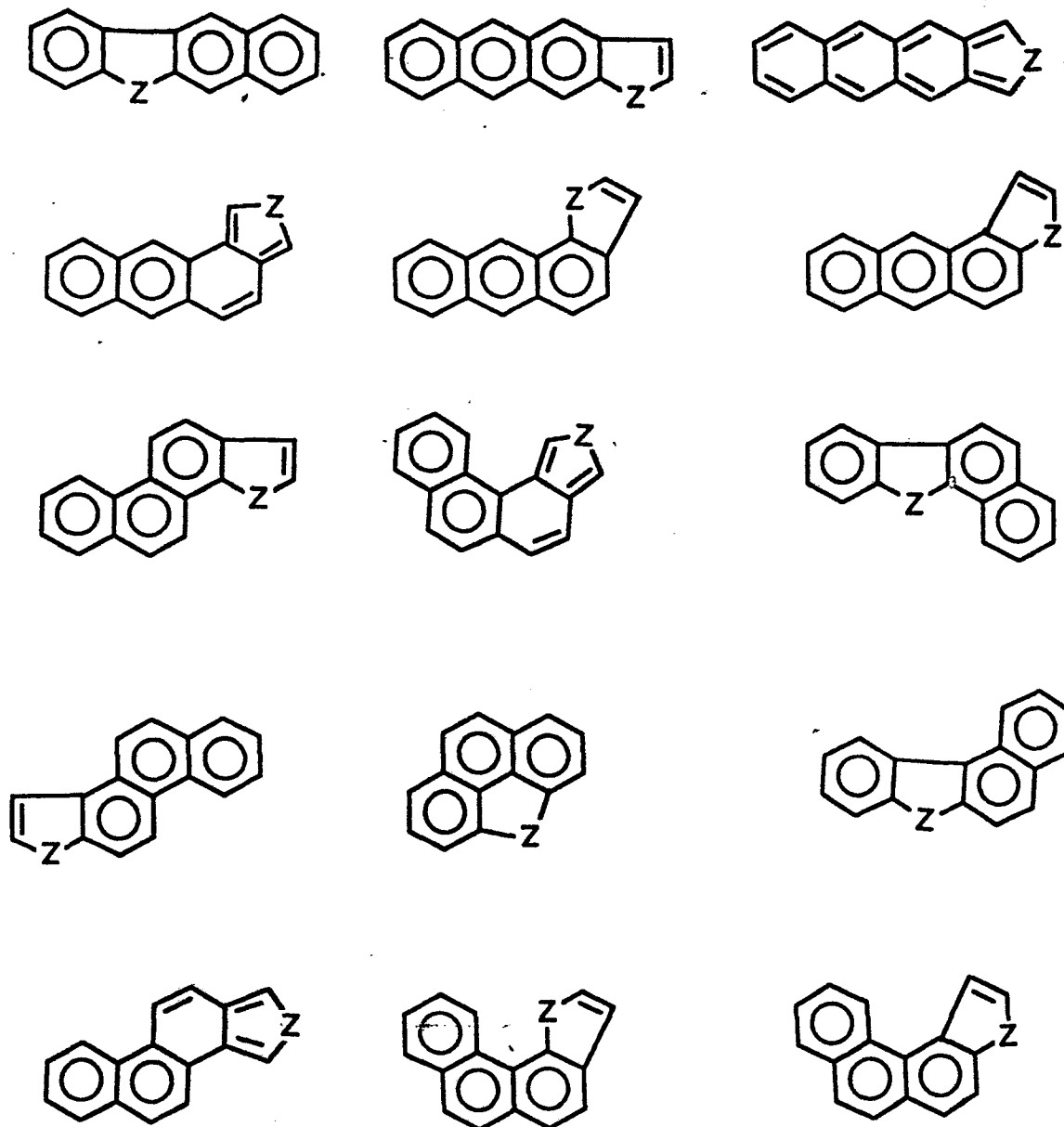
6,6,6,5 N-Containing Ring Systems



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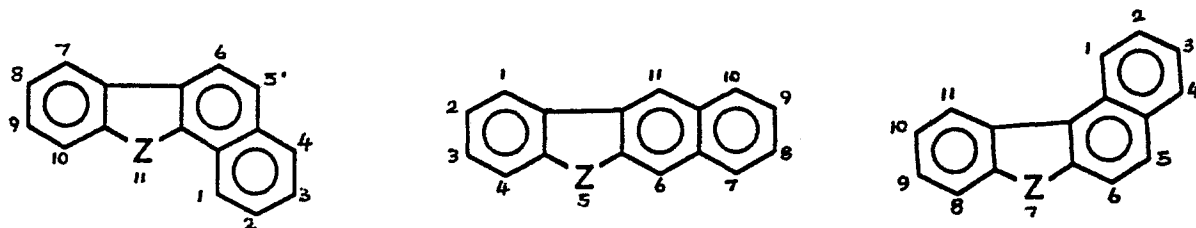
One preferred group of compounds of the present invention is that in which Ar is a ring system having 15 or 17 ring atoms.

Suitably Ar is selected from one of the following ring systems:



wherein Z is a heteroatom.

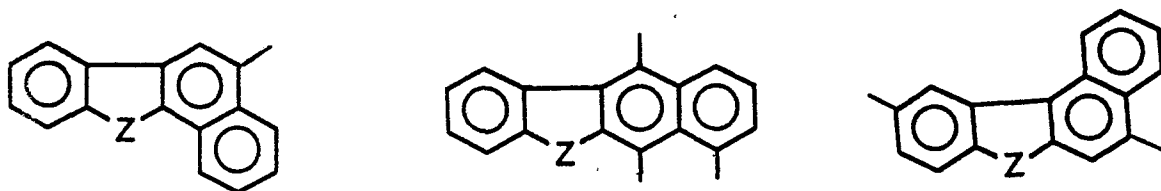
One particularly preferred group of compounds of the formula (I) is that in which Ar is selected from:



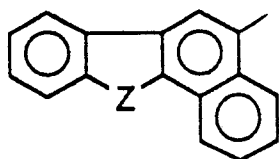
These ring systems have the following nomenclature:

	Z=NH	
11- <u>H</u> -Benzo[<u>a</u>]carbazole	5- <u>H</u> -Benzo[<u>b</u>]carbazole	7- <u>H</u> -Benzo[<u>c</u>]carbazole
	Z=O	
Benzo[<u>b</u>]naphtho[2,1- <u>d</u>] furan	Benzo[<u>b</u>]naphtho[2,3- <u>d</u>] furan	Benzo[<u>b</u>]naphtho[1,2- <u>d</u>] furan
	Z=S	
Benzo[<u>b</u>]naphtho[2,1- <u>d</u>] thiophene	Benzo[<u>b</u>]naphtho[2,3- <u>d</u>] thiophene	Benzo[<u>b</u>]naphtho[1,2- <u>d</u>] thiophene

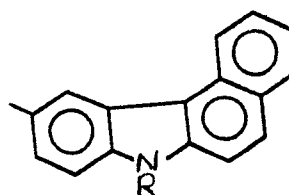
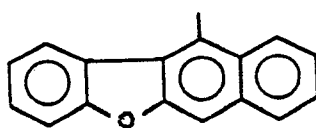
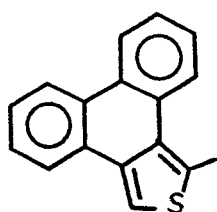
Preferably the CH_2NHR^1 side chain is attached at one of the positions indicated below.



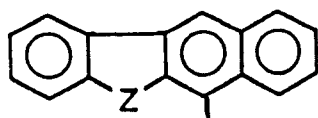
Suitably Ar is selected from



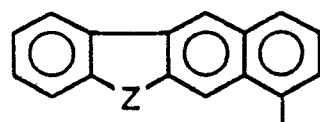
wherein Z = O, S,
NMe or NEt



where R=Me or Et



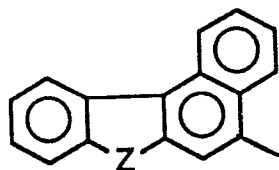
or



wherein Z= S or O

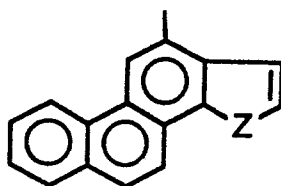
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and



wherein Z= S,O,
NMe, or NEt

A further preferred group of compounds of the formula (I) is that in which Ar is:



wherein Z= S,O,NMe or NEt

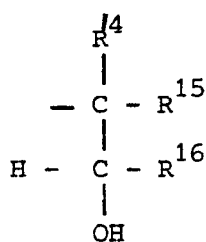
Preferably Ar is 7H-benzo[c]carbazol-10-yl or benzo[b]naphtho[2,1-d]furan-5-yl.

Suitably the aromatic ring is unsubstituted or has only one substituent.
Preferably the aromatic ring is unsubstituted.

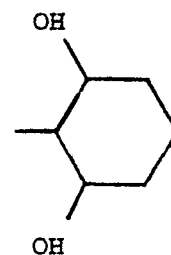
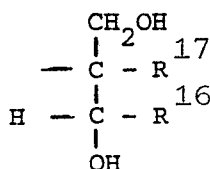
Suitably $\text{ArCH}_2\text{NHR}^1$ or a monomethyl or monoethyl ether thereof contains not more than 28 carbon atoms in total.

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Suitably m is 0.

Suitably R¹ is

or

wherein R¹⁴ is CH₂OH, CH(CH₃)OH or CH₂CH₂OH;R¹⁵ is hydrogen, C₁₋₃ alkyl or CH₂OH;R¹⁶ is hydrogen or methyl.Suitably R¹⁴ is CH₂OH or CH(CH₃)OH. Suitably R¹⁵ is hydrogen, methyl, ethyl or CH₂OH.Preferably R¹ iswherein R¹⁶ is hydrogen or methyl and R¹⁷ is hydrogen, methyl or ethyl, most preferably methyl.

Specific compounds within the scope of formula (I) include;

2-[(9-Benzo[b]naphtho[2,1-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[(Benzo[b]naphtho[2,3-d]furan-6-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[(Benzo[b]naphtho[1,2-d]furan-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[(Benzo[b]naphtho[2,1-d]furan-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-Methyl-2-[(7-methyl-7H-benzo[c]carbazol-10-yl)methyl]amino]-1,3-propanediol
 2-[(Benzo[b]naphtho[2,3-d]thiophen-6-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-(5-Ethyl-(benzo[b]carbazol-7-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-(Benzo[b]naphtho[2,3-d]furan-11-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-(Benzo[b]naphtho[2,3-d]thiophen-8-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-[(5-Ethyl)-benzo[b]carbazol-6-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-[(Benzo[b]naphtho[2,3-d]thiophen-7-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-[(Phenanthro[9,10-c]thiophen-1-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-Methyl-2-[(phenanthro[9,10-b]furan-2-ylmethyl)amino]-1,3-propanediol

2-[(Benzo**b**naphtho[1,2-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-Methyl-2-[(phenanthro[4,3-b]furan-2-ylmethyl)amino]-1,3-propanediol
 2-[(Phenanthro[1,2-b]thiophen-2-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-Methyl-2-[(phenanthro[1,2-b]furan-2-ylmethyl)amino]-1,3-propanediol
 2-Methyl-2-[(phenanthro[4,3-b]thiophen-7-ylmethyl)amino]-1,3-propanediol
 2-[(Phenanthro[1,2-b]thiophen-4-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[(Phenanthro[1,2-b]furan-4-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[Benzo**b**naphtho[2,3-d]furan-7-ylmethyl)amino]-2-methyl-1,3-propanediol
 and monomethyl or monoethyl ethers, esters, and acid addition salts thereof.

Of these specific examples of compounds of formula (I) preferred compounds include 2-methyl-2-[(7-methyl-7H-benzo**c**carbazol-10-yl)methyl]amino-1,3-propanediol and 2-[(benzo**b**naphtho[2,1-d]furan-5-ylmethyl)amino]-2-methyl-1,3-propanediol and monomethyl or monoethyl ethers, esters and acid addition salts thereof.

Salts included within the scope of the present invention are those of compounds of formula (I) and ethers and esters thereof.

Esters and non-pharmaceutically useful salts of the compounds of the formula (I) are useful intermediates in the preparation and purification of compounds of the formula (I) and pharmaceutically useful salts thereof, and are therefore within the scope of the present invention. Thus, salts of the compounds of the formula (I) useful in the present invention include but are not limited to those derived from inorganic acids, such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids such as isethionic (2-hydroxyethylsulfonic), maleic, malonic, succinic, salicylic, tartaric, lactic, citric, formic, lactobionic, pantothenic, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, naphthalene-2-sulfonic, and ascorbic acids, and amino acids such as glycine. Pharmacologically and pharmaceutically acceptable salts are preferred, particularly those that are soluble in solvents suitable for parenteral administration, for example, hydrochlorides, methanesulfonates and isethionates.

Esters of compounds of formula (I) are derived from acids known to those skilled in the art to be suitable for ester formation, and are conveniently those derived from C₁₋₆ alkanolic acids or alkanolic acid derivatives, for example acetic acid, propionic acid, *n*-butyric acid and *iso*-butyric acid. The esters may be formed from all or only some of the hydroxy groups contained in the compounds of formula (I).

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The compounds of formula (I) and their ethers, esters, and salts thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure. Thus, the compounds of formula (I) may, for example, be prepared by any of the methods defined below.

1. The reduction of a compound ArCH=NR^1 (II)

wherein Ar and R^1 are as hereinbefore defined, or an appropriately protected derivative thereof followed by deprotection where appropriate.

The conditions and reagents for such a reaction are well known to those skilled in the art, and any such conditions/reagents may be employed that will not reduce the aromatic ring system. The conversion of (II) or suitably protected derivatives thereof may be carried out by a reducing agent followed by deprotection if necessary. The reduction is conveniently carried out by a metal hydride such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, or by catalytic hydrogenation, conveniently by hydrogen in the presence of a metal catalyst such as palladium or platinum, or equivalent reagents as outlined by J. March, Advanced Organic Chemistry, 2nd ed., pages 819-820, McGraw Hill, New York, 1977. The reduction is suitably carried out with Ar-CH=NR^1 in solution in an inert solvent or mixture of solvents compatible with the reducing agent, at a non-extreme temperature, for example, between 0° and 80°C , conveniently at room temperature.

In the case of lithium aluminum hydride and like reagents, suitable solvents include ethers (for example tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane) optionally in the presence of a hydrocarbon cosolvent (for example toluene, benzene or hexane).

In the case of sodium borohydride and like reagents, suitable solvents include alcohols (for example ethanol, methanol or isopropanol) optionally in the presence of a hydrocarbon cosolvent (for example toluene, benzene or hexane) or an ether cosolvent (for example diethylether or tetrahydrofuran).

In the case of sodium cyanoborohydride and like reagents, suitable solvents include those described for sodium borohydride and the reduction is conveniently carried out in the presence of an acid, conveniently glacial acetic acid or ethanolic hydrochloric acid as outlined in, for example, R. Hutchins et al., Organic Preparations and Procedures International 11, 201 (1979).

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In the case of catalytic hydrogenation, suitable solvents include alcohols (for example methanol and ethanol) optionally in the presence of a hydrocarbon cosolvent (for example toluene or benzene), or ether cosolvent (for example diethyl ether or tetrahydrofuran) optionally in the presence of an acid (for example glacial acetic acid or ethanolic hydrochloric acid), or glacial acetic acid.

Protected derivatives of compounds ArCH=NR^1 are conveniently used when lithium aluminum hydride is employed as the reducing agent. Convenient protecting groups are compatible with the reducing agent utilized and are readily removed under nondestructive conditions, for example benzyl, tetrahydropyranyl and isopropylidene ethers.

It is often convenient not to isolate the compound ArCH=NR^1 but to react a compound ArCHO with a compound NH_2R^1 ; wherein Ar and R^1 are as defined in (I) and to reduce the compound of the formula ArCH=NR^1 so formed in situ. The reaction of the compounds ArCHO and NH_2R^1 is again suitably carried out using conditions and reagents which are well known to those skilled in the art, for example in the presence of an acid, such as a sulfonic acid, i.e. p-toluenesulfonic acid, in an appropriate inert solvent, such as an aromatic hydrocarbon, suitably toluene, with azeotropic removal of water followed by treatment with the reducing agent in an appropriate solvent, suitably ethanol or methanol. Alternatively, ArCH=NR^1 formed under equilibrium conditions in appropriate solvents can be reduced in situ with an appropriate reducing agent, suitably sodium cyanoborohydride.

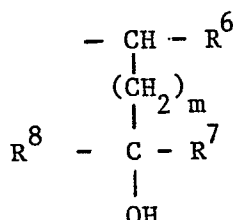
The compound ArCHO may be in the form of a protected aldehyde, for example an acetal, which liberates the aldehyde function under the reaction conditions. In turn, a compound ArCHO can be synthesized by reacting the appropriate polycyclic aromatic hydrocarbon with a formylating agent such as that generated by the reaction between SnCl_4 and $\text{Cl}_2\text{CHOCH}_3$ or equivalent reagents, for example, according to the method of A. Reiche *et al.*, Chem. Ber. **93**, 88 (1960), or with other standard formylating reagents/procedures known to the art, for example, the Gatterman-Koch reaction ($\text{CO/HCl/AlCl}_3/\text{CuCl}$), the Gatterman reaction (HCN/HCl/ZnCl_2), and the Vilsmeier reaction ($\text{POCl}_3/\text{PhN(Me)CHO}$ or $\text{POCl}_3/\text{Me}_2\text{NCHO}$) (J. March, vide supra pages 494-497).

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The compounds ArCHO may also be prepared from an appropriate aromatic heteropolycycle substituted by a suitable functional group and converting this functional group to an aldehyde group by methods well known to those skilled in the art. Suitable functional groups include CHBr_2 , CH_3 , COR^{19} wherein R^{19} is a primary or secondary C_{1-6} alkyl group, COOH or a derivative thereof such as an ester, amide, or acid chloride, or CN .

Where the aromatic heteropolycycle bears substituents, ArCHO may be prepared by a variety of methods known in the art of organic chemistry depending on the nature of the substituent on the ring. For example, if the substituent(s) is a halogen, the starting materials may be prepared by direct treatment of the aromatic heteropolycycle with a halogenating agent (e.g. Cl_2 , Br_2 , or SO_2Cl_2) or indirectly by such routes as the Sandmeyer reaction (H.H. Hodgson, Chem. Rev. **40**, 251 (1947)). If the substituent(s) is alkyl, the aromatic heteropolycycle may be reacted with the appropriate reagents under Friedel-Crafts reaction conditions (G.A. Olah, Friedel Crafts and Related Reactions, Vols. 1-3, Interscience, New York, NY, 1963-1965).

The compounds of the formula NH_2R^1 also may be prepared by methods known in the art, for example, when R^1 is as hereinbefore defined, by the reaction of NO_2R^{18} , wherein R^{18} is



wherein R^6 to R^8 and m are as hereinbefore defined, with an appropriate aldehyde, conveniently acetaldehyde or formaldehyde (as in B.M. Vanderbilt and H.B. Hass, Ind. Eng. Chem. **32**, 34 (1940)) followed by reduction (as outlined in J. March, vide supra, pages 1125-1126), conveniently by hydrogen and a metal catalyst (for example, a platinum containing catalyst) in an appropriate solvent, conveniently glacial acetic acid.

2. The reduction of a compound Ar. CO. NHR^1

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wherein Ar and R^1 are as hereinbefore defined and the hydroxy groups are optionally protected, followed by deprotection of the hydroxy groups where appropriate. The reduction may be carried out by standard reducing agents known for carrying out this type of reduction that will not reduce the aromatic ring system (as outlined in J. March, vide supra, page 1122), for example, a hydride reagent such as lithium aluminium hydride in an inert solvent, such as an ether, i.e. tetrahydrofuran, at a non-extreme temperature, for example, at between 0° and 100°C and conveniently at the reflux temperature of the ether.

The compound $\text{Ar} \cdot \text{CO} \cdot \text{NHR}^1$ may be formed by the reaction of the appropriate acid (ArCOOH) or a suitable reactive acid derivative thereof as outlined in J. March, vide supra, pages 382-390) for example, an acid halide in an inert solvent, with an amine NH_2R^1 in which the hydroxy groups are optionally protected, for example, when the compound NH_2R^1 is a diol, by an isopropylidene group. The compound $\text{Ar} \cdot \text{CO} \cdot \text{NHR}^1$ so formed is suitably reduced in situ and deprotected if necessary to give a compound of formula (I). The compounds of the formula ArCOOH can be prepared by methods well known to those skilled in the art.

3. The reaction of a compound ArCH_2L (wherein Ar is as hereinbefore defined and L is a leaving group), with a compound NH_2R^1 as hereinbefore defined. Suitable leaving groups are those defined by J. March, vide supra pages 325-331, and include halogens such as chlorine or bromine and sulfonic acid derivatives such as *p*-toluenesulfonate. The reaction is suitably carried out in an appropriate solvent, such as a dipolar aprotic solvent or alcohol at a non-extreme temperature, for example 50 - 100° . The compounds of the formula ArCH_2L can be prepared by methods well known to those skilled in the art.

There is therefore provided, as a further aspect of the invention, a method for the preparation of a compound of formula (I) comprising any method known for the preparation of analogous compounds, in particular those methods defined in (1) to (3) hereinabove.

In a further aspect, the present invention provides novel chemical intermediates $\text{ArCH}=\text{NR}^1$, $\text{Ar} \cdot \text{CO} \cdot \text{NHR}^1$ or ArCH_2L as herein before defined. Compounds of the formula (I) in which one or more of the hydroxy groups are protected, for example by benzyl, trityl or isopropylidene groups are also useful intermediates of the present invention.

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The compounds of this invention have biocidal activity, e.g. are toxic to certain living cells which are detrimental to mammals, for example pathogenic organisms and tumours.

This toxicity to pathogenic organisms has been demonstrated for example, by activity against one or more of the following: viruses (e.g. Herpes simplex 1/vero), fungi (e.g. Candida albicans), protozoa (e.g. Eimeria tenella and Trichomonas vaginalis), bacteria (e.g. Mycoplasma smeg matis and Streptococcus pyogenes), and helminths (e.g. Nippostrongylus brasiliensis and Brugia pahangi). The antitumour activity of compounds of formula I has been demonstrated in a number of recognized screens and primarily by activity against ascitic P388/O leukaemia.

Preferred compounds of the formula (I) are those which have antitumour activity. The activity against ascitic tumours, including P388/O, is evidenced by reduction of tumour cell number in mammals (for example, mice bearing ascitic tumours) and their consequent increase in survival duration as compared to an untreated tumour bearing control group. Antitumour activity is further evidenced by measurable reduction in the size of solid tumours following treatment of mammals with the compounds of this invention compared to the tumours of untreated control tumour bearing animals. Compounds of formula (I) are active against murine tumours such as lymphocytic leukaemia P388/O, lymphocytic leukaemia L1210, melanotic melanoma B16, P815 mastocytoma, MDAY/D2 fibrosarcoma, colon 38 adenocarcinoma, M5076 rhabdomyosarcoma and Lewis lung carcinoma.

Activity in one or more of these tumour tests has been reported to be indicative of antitumour activity in man (A. Goldin et al. in Methods in Cancer Research ed. V.T. DeVita Jr. and H. Busch, 16, 165, Academic Press, N.Y. 1979).

There are sublines of P388/O which have been made resistant to the following clinically useful agents: cytosine arabinoside, doxorubicin, cyclophosphamide, L-phenylalanine mustard, methotrexate, 5-fluorouracil, actinomycin D, cis-platin and bis-chloroethylnitrosourea. Compounds of this invention show potent activity against these drug-resistant tumours using the procedure for P388/O above.

Compounds of formula (I) have also been found to be active against human tumour cells in primary cultures of lung, ovary, breast, renal, melanoma,

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unknown primary, gastric, pancreatic, mesothelioma, myeloma, and/or colon cancer. (As used herein "cancer" is to be taken as synonymous with "malignant tumour" or more generally "tumour" unless otherwise noted.) This is a procedure in which the prevention of tumour cell colony formation, i.e. tumour cell replication, by a drug has been shown to correlate with clinical antitumour activity in man (D.D. Von Hoff et al., Cancer Chemotherapy and Pharmacology 6, 265 (1980); S. Salmon and D.D. Von Hoff, Seminars in Oncology, 8, 377 (1981)).

Compounds of formula I which have been found to have antitumour activity intercalate in vitro with DNA (this property is determined by viscometric methods using the procedure of W. D. Wilson et al., Nucleic Acids Research 4, 2697 (1954)) and have a log P as calculated by the method of C. Hansch and A. Leo in Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley and Sons, New York, 1979, lying in the range between -2.0 and +2.5.

As has been described above, the compounds of the present invention are useful for the treatment of tumours. The invention thus further provides a method for the treatment of tumours in animals, including mammals, especially humans, which comprises the administration of a clinically useful amount of compound of formula (I) in a pharmaceutically useful form, once or several times a day or other appropriate schedule, orally, rectally, parenterally, or applied topically. In addition, there is provided as a further, or alternative, aspect of the invention, a compound of formula (I) for use in therapy, for example as an antitumour agent.

The amount of compound of formula (I) required to be effective as a biocidal agent will, of course, vary and is ultimately at the discretion of the medical or veterinary practitioner. The factors to be considered include the condition being treated, the route of administration, and nature of the formulation, the mammal's body weight, surface area, age and general condition, and the particular compound to be administered. A suitable effective antitumour dose is in the range of about 0.1 to about 120 mg/kg body weight, preferably in the range of about 1.5 to 50 mg/kg, for example 10 to 30 mg/kg. The total daily dose may be given as a single dose, multiple doses, e.g., two to six times per day

or by intravenous infusion for selected duration. For example, for a 75 kg mammal, the dose range would be about 8 to 9000 mg per day, and a typical dose would be about 2000 mg per day. If discrete multiple doses are indicated, treatment might typically be 500 mg of a compound of formula I given 4 times per day in a pharmaceutically useful formulation.

Whilst it is possible for the active compound (defined herein as compound of formula (I), or ether, ester, or salt thereof) to be administered alone, it is preferable to present the active compound in a pharmaceutical formulation. Formulations of the present invention, for medical use, comprise an active compound together with one or more pharmaceutically acceptable carriers thereof and optionally other therapeutical ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention, therefore, further provides a pharmaceutical formulation comprising a compound of formula (I) (in the form of the free base, ether, or ester derivative or a pharmaceutically acceptable acid addition salt thereof) together with a pharmaceutically acceptable carrier therefor.

There is also provided a method for the preparation of a pharmaceutical formulation comprising bringing into association a compound of formula (I) an ether, ester, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor.

Whilst the antitumour activity of the compounds of formula (I) is believed to reside in the free base, it is often convenient to administer an acid addition salt of a compound of formula (I).

The formulations include those suitable for oral, rectal or parenteral (including subcutaneous, intramuscular and intravenous) administration. Preferred formulations are those suitable for oral or parenteral administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier

which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier or both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, a mixture of the powdered active compound with any suitable carrier.

A syrup may be made by adding the active compound to a concentrated, aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredients. Such accessory ingredient(s) may include flavourings, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol for example glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a conventional carrier such as cocoa butter.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Such formulations suitably comprise a solution of a pharmaceutically and pharmacologically acceptable acid addition salt of a compound of the formula (I) that is isotonic with the blood of the recipient. Thus, such formulations may conveniently contain distilled water, 5% dextrose in distilled water or saline and a pharmaceutically and pharmacologically acceptable acid addition salt of a compound of the formula (I) that has an appropriate solubility in these solvents, for example the hydrochloride, isethionate and methanesulfonate salts, preferably the latter.

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Useful formulations also comprise concentrated solutions or solids containing the compound of formula (I) which upon dilution with an appropriate solvent give a solution suitable for parenteral administration as above.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The following examples are provided by the way of illustration of the present invention and should in no way be construed as a limitation thereof.

General Comments

All solvents were reagent grade and used without further purification with the following exceptions. Tetrahydrofuran (THF) was dried by distillation from Na/K alloy under nitrogen (N_2) and used immediately. Toluene ($PhCH_3$) was distilled from CaH_2 under N_2 and stored over 3A molecular sieves. Chemicals used were reagent grade and used without purification unless noted. The full name and address of the suppliers of the reagents and chemicals is given when first cited. After this, an abbreviated name is used.

Preparative HPLC was carried out on a Waters Prep LC/System 500A machine using two 500 g silica gel (SiO_2) cartridges unless otherwise noted. Plugs of SiO_2 used for purifications were "flash chromatography" silica gel (Merck Co., Inc., Merck Chemical Division, Rahway, NJ, 07065 silica gel 60, 230-400 mesh). An appropriate volume sintered glass funnel was filled approximately 3/4 full with the silica gel and packed evenly by tapping the outside of the funnel. A piece of filter paper was then placed on top of the silica gel and a solution of the material to be purified applied evenly to the top. Gentle suction through a filter flask moved the eluting solvent through the plug rapidly. The appropriate size fractions were combined as needed and further manipulated.

General procedures are described in detail. Analogous procedures show melting point (mp), recrystallization solvents, and elemental analyses (all elements analyzing within a difference of $\pm 0.4\%$ of the expected value). Any changes to the procedure such as solvent, reaction temperature, reaction time, or workup are noted.

NMR (^1H , ^{13}C), IR, MS data of all new products were consistent with the expected and proposed structures. The positions assigned to structural isomers were unequivocally determined by a number of NMR techniques. All final products were dried in a vacuum oven at 20 mm Hg pressure at the temperature indicated overnight (12-16 hours). All temperatures are in degrees Celsius.

EXAMPLE 1

2-((Benzo[b]naphtho[2,1-d]thiophen-5-ylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate

To a round bottomed flask equipped with magnetic stirring bar, condenser, thermometer, Dean-Stark trap, and nitrogen inlet and bubbler was added benzo[b]naphtho[2,1-d]thiophene-5-carbaldehyde, (SISA Pharmaceutical Laboratories, Inc; 763 Concord Avenue, Cambridge, MA, 02138, 4.94g, 18.83 mmol), 2-amino-2-methyl-1,3-propanediol (Aldrich, 1.98g, 18.83 mmol), p-toluenesulfonic acid monohydrate (Aldrich, 0.1g) and toluene (200 mL). The mixture was stirred at reflux with removal of water for 2.5h (or until no water is formed which was extracted with ethyl acetate (3x500 mL). The ethyl acetate collected). Most of the toluene was then removed by distillation. The mixture was then cooled in an ice bath and diluted with abs. ethanol (200 mL) and further cooled. Solid sodium borohydride (MCB Manufacturing Chemists, Inc., 2909 Highland Ave., Cincinnati, OH, 45212, 0.712g, 18.83 mmol) was added in one portion to the reaction mixture. The ice bath was then removed, the reaction mixture allowed to warm to room temperature and then stirred overnight. The reaction was then acidified with 10% hydrochloric acid and the solvents removed by rotary evaporation. The crude solid was shaken with 1N hydrochloric acid (300 mL) filtered, washed with hydrochloric acid, sucked semidry and washed with diethyl ether (300 mL). The material was dissolved in methanol (200 mL), filtered and basified with 1N sodium hydroxide solution (1L). A white solid washings were combined, filtered, washed with satd. sodium chloride (3x500 mL), dried with potassium carbonate (Mallinkrodt, 25g), filtered, and concentrated by rotary evaporation to give a white solid. This was dissolved in a mixture of abs.

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ethanol (200 mL) and methanesulphonic acid (99.5%, Morton Thiokol, Inc. - Alfa Products, PO Box 299, 152 Andover Street, Danvers, MA, 01923, 3 mL), filtered and diluted to 4L with a mixture of diethyl ether/hexane (1:1). This material was recrystallized three times from ethanol/hexane (1:3) to give 2-((benzo[b]naphtho[2,1-d]thiophen-5-ylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate mp 221-222° which analysed correctly for the assigned structure (C₂₁H₂₅N₂S₂O₃).

EXAMPLE 2

2-((Benzo[b]naphtho[2,3-d]furan-6-ylmethyl)amino)-2-methyl-1,3-propanediol

2A Benzo[b]naphtho[2,3-d]furan-6-carbaldehyde

Benzo[b]naphtho[2,3-d]furan (SISA) was formylated using the procedure of A. Rieche *et al*, Chem. Ber. 93, 88(1960). The crude aldehyde appeared to be mainly one isomer by TLC. Purification by chromatography, silica gel, toluene followed by recrystallization (methylene dichloride/hexane) gave pure material (58% yield) identified using NMR techniques to be benzo[b]naphtho[2,3-d]furan-6-carbaldehyde mp 169-171.5°. The product analysed correctly for the assigned structure (C₁₅H₉).

2B. 2-((Benzo[b]naphtho[2,3-d]furan-6-ylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate

Using the reductive amination procedure described in exmple 1, benzo[b]naphtho[2,3-d]furan-6-carbaldehyde (2A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-((benzo[b]naphtho[2,3-d]furan-6-ylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate 0.4 H₂O mp 187-190°, (EtOH/Et₂O) which analysed correctly for the assigned structure (C₂₁H₂₅N₂S₂O₃).

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EXAMPLE 32-((Benzo[b]naphtho[1,2-d]furan-5-ylmethyl)amino)-2-methyl-1,3-propanediol3A Benzo[b]naphtho[1,2-d]furan-5-carbaldehyde.

Benzo[b]naphtho[1,2-d]furan (SISA) was formylated using the procedure of A. Rieche *et al*, Chem. Ber. 93, 88 (1960). The crude aldehyde appeared to be only one isomer by TLC. Purification by chromatography (silica, toluene) followed by recrystallization (methylene dichloride/hexane) gave pure material (39% yield), identified using NMR techniques to be benzo[b]-naphtho[1,2-d]furan-5-carbaldehyde mp 143-145°. The product analysed correctly for the assigned structure (C, H).

3B 2-((Benzo[b]naphtho[1,2-d]furan-5-ylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate

Using the reductive amination procedure described in example 1, benzo[b]naphtho[1,2-d]furan-5-carbaldehyde (3A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-((benzo[b]naphtho[1,2-d]furan-5-ylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate mp 215-217°, (EtOH/Et₂O) which analysed correctly for the assigned structure (C,H,N,S).

Example 42-Methyl-2-(((7-methyl-7H-benzo[c]-carbazol-10-yl)methyl)amino)-1,3-propanediol4A 7-Methyl-7H-benzo[c]carbazole

7H-Benzo[c]carbazole (6.6g) (ex. PARS) was dissolved in tetrahydrofuran (250mL) under nitrogen and treated with potassium t-butoxide (4.2g). Once this had dissolved, dimethylsulphate (7.56g) was added and the mixture stirred for several minutes after which time TLC (silica/toluene) showed the reaction to be complete. The reaction mixture was poured into 1N sodium hydroxide (2L) and stirred. The solid so formed was collected by filtration, taken up in toluene (300mL) and eluted through a plug of silica

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(2"x2") with toluene. The product containing fractions were evaporated to dryness, the solid dissolved in methylene chloride (400mL) and diluted with hexane. Concentration under vacuum gave a white solid (5.0g) which was filtered and washed with pentane. A further 1.06g of product (total yield 6.06g, 87%) was obtained on standing and further concentration of the filtrate. Analysis $C_{17}H_{13}N$ calculated: C, 88.28; H, 5.67, N; 6.06%, found: C, 88.31; H 5.68; N 6.01%.

4B 7-Methyl-7-H-benzo[c]carbazole-10-carbaldehyde

7-Methyl-7-H-benzo[c]carbazole (5.8g) was dissolved in methylene chloride and treated with stannic chloride (13.0g) under nitrogen. The mixture was cooled and α,α -dichloromethyl methyl ether (3.74g) was added dropwise. The reaction was stirred at RT for 4 hours, then heated to reflux for 15 minutes. TLC (silica/toluene) showed complete reaction; the reaction mixture was cooled, water (300mL) added and the mixture stirred for 2 hours. The 2-phase mixture was filtered and the organic layer isolated and evaporated to dryness. The residue was dissolved in toluene (100mL) and eluted through a plug of silica (5"x3") with toluene. The ninth litre eluted contained the major isomer present and this and the tenth litre (eluted with dichloromethane) were combined and evaporated to dryness. The residue was taken up in dichloromethane (200mL), filtered and diluted 1:1 with pentane. The solution was evaporated until crystallisation began. Further pentane was added and the volume reduced to 150mL. Filtration afforded the title product (3.83g) as a pale yellow solid, m.p. 164-165°, pure by t.l.c. Analysis $C_{18}H_{13}NO$ calculated: C, 83.37; H, 5.05; N, 5.40%; found: C, 83.19; H, 5.07; N, 5.36%.

The 3rd through 8th litres eluted from the silica plug above were combined and evaporated to dryness. The solid was taken up in dichloromethane (200mL), then diluted with hexane (200mL). Evaporation of the solvent gave a yellow solid which was dissolved in dichloromethane (200mL), diluted with hexane (200mL) and concentrated to give a crystalline yellow solid (0.55g) which was identified by NMR as 7-methyl-7-H-benzo[c]carbazole-5-carbaldehyde, m.p. 210-213°. Analysis $C_{18}H_{13}NO$ calculated: C, 83.37; H, 5.05; N, 5.40%; found: C, 83.43; H, 5.08; N, 5.37%.

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- 4C 2-Methyl-2-[[[(7-methyl-7-H-benzo[c] carbazol-10-yl) methyl]amino-1,3-propanediol hydrochloride 3/10 hydrate.

The title compound (4) was prepared by a method analogous to Example 1 from 7-methyl-7H-benzo[c]carbazole-10-carbaldehyde and 2-amino-2-methyl-1,3-propanediol, m.p. 229-230° (dec)(MeOH:Et₂O/1:3). Analysis C₂₂H₁₅N₂O₂Cl₃/10H₂O calculated; C, 67.70; H, 6.61; N, 7.18; Cl, 9.08%; found: C, 67.61; H, 6.53; N, 7.17; Cl, 9.05%. NMR spectrum was consistent with this structure.

Example 5

2-[(Benzo[b]naphtho[2,1-d]furan-5-yl)methyl]amino-2-methyl-1,3-propanediol

- 5A Benzo [b]naphtho[2,1-d]furan-5-carboxaldehyde

Benzo[b]naphtho[2,1-d]furan (6.15g, PARS) was dissolved in methylene chloride (400mL) under nitrogen. Stannic chloride (14.59g) was added followed by α,α-dichloromethyl methyl ether (4.02g), and the resulting mixture stirred overnight and then refluxed for 3 minutes. Water (200mL) was added and the mixture stirred overnight. The organic layer was separated and evaporated to dryness. The residue was dissolved in toluene (200mL) and eluted through a plug of silica (3 1/2 " x 3") with toluene. The product fractions were collected, evaporated to dryness, redissolved in methylene chloride (200mL), diluted with pentane (500mL) and concentrated to 150mL. Additional pentane (200mL) was added to the precipitate which was then filtered to give the title compound (5.0g), m.p. 118-121°. A further 0.34g of product was isolated from the filtrate. Analysis C₁₇H₁₀O₂ calculated: C, 82.91; H, 4.09%, found: C, 83.00; H, 4.13%. NMR spectrum consistent with structure.

- 5B 2-[(Benzo[b]naphtho[2,1-d]furan-5-yl)methyl]amino-2-methyl-1,3-propanediol
The title compound was prepared as its methanesulphonate salt(s) by a method analogous to example 1 from benzo[b]naphtho[2,1-d]furan-5-carboxaldehyde and 2-methyl-1,3-propanediol, m.p. 216-218° (EtOH:Et₂O/1:4). Analysis C₂₂H₂₅NO₆S calculated: C, 60.23; H, 5.93; N, 3.19; S, 7.31%; found: C, 60.22; H, 5.93; N, 3.18; S, 7.30% NMR spectrum was consistent with structure.

Example 62-[(Benzo[b]naphtho[2,3-d]furan-7-ylmethyl)amino]-2-methyl-1,3-propanediol6A 7-Bromomethyl-benzo[b]naphthol[2,3-d]furan

To a round bottom flask was added 7-methyl-benzo[b]naphtho-[2,3-d]furan (16.0g, 0.07 mol, ex. Pars), N-bromosuccinimide (12.8g, 0.072 mol), a catalytic amount of benzoyl peroxide (0.01g) and carbon tetrachloride (1L). The mixture was refluxed for 2.5 hours, cooled and filtered to remove the succinimide formed in the reaction. The solvent was then removed from the reaction mixture by rotary evaporation. The crude product was purified by flash chromatography on silica gel using toluene as the eluting solvent. The appropriate fractions were combined and the solvent once again removed by rotary evaporation to give 22.0g of product. The material (which was one spot by thin layer chromatography and pure by NMR) was used without further purification.

6B 2-[(Benzo[b]naphthol[2,3-d]furan-7-ylmethyl)amino]-2-methyl-1,3-propanediol methanesulphonate 1/4 hydrate

To a round bottom flask was added 7-bromomethyl-benzo[b]naththol[2,3-d]furan (22.0g, 0.0706 mol), potassium carbonate (19.49g, 0.141 mol) and absolute ethanol (600 mL). The mixture was refluxed overnight, cooled and filtered. The solvent was then removed by rotary evaporation to give a white residue. This was shaken with hot water (500 mL). The mixture was allowed to stand at room temperature for 1 hour and the resulting solid filtered. The mixture was filtered and the resulting solid washed twice with warm water (500 mL.) The damp solid was dissolved in absolute ethanol (400 mL) containing methanesulphonic acid (3 mL). The liquid was filtered through a fine fritted glass funnel and the filtrate diluted to 2L with ether. The resulting solid was filtered and recrystallised twice from absolute ethanol/ether (1/2). After drying in a vacuum oven overnight at 80°, 9.67g of the title compound (6) (32%) m.p. 248-249° (dec) was obtained. Analysis $C_{22}H_{25}NO_6S \cdot 1/4H_2O$ calculated: C,60.48; H,5.95; N,3.17; S,7.30%, found; C,60.60; H,5.89; N,3.21; S,7.35%.

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Example 72-[(Benzo[b]naphtho[2,3-d]thiophen-6-ylmethyl)amino]-2-methyl-1,3-propanediol7A Benzo[b]naphtho[2,3-d]thiophene-6-carbaldehyde

Using the procedure outlined in example 2B benzo[b]naphtho[2,3-d]thiophene (Cambridge Chemical, Inc. gave benzo[b]naphtho[2,3-d]thiophene-6-carbaldehyde, mp 199° in 80.1% yield which analyzed correctly (C,H,S) for the assigned structure.

7B 2-[(Benzo[b]naphtho[2,3-d]thiophen-6-ylmethyl)amino]-2-methyl-1,3-propanediol methanesulfonate

Using the procedure outlined in example 1, benzo[b]naphtho[2,3-d]thiophene-6-carbaldehyde (7A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-[(benzo[b]naphtho[2,3-d]thiophen-6-yl-methyl)amino]-2-methyl-1,3-propanediol methanesulfonate, mp 242-243° in 67.1% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 82-[(Benzo[b]naphtho[2,3-d]thiophen-8-ylmethyl)amino]-2-methyl-1,3-propanediol8A Benzo[b]naphtho[2,3-d]thiophene-8-carbaldehyde

To a round bottom flask equipped with magnetic stirring bar, reflux condenser and N₂ inlet line was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Aldrich, 38.6g, 0.119 mol), H₂O (100 mL) and CHCl₃ (1500mL). After refluxing the mixture for 15 minutes 8-methylbenzo[b]naphtho-[2,3-d]thiophene (Cambridge Chemicals, Inc., 21.0g, 89.6 mmol) was added to the flask. The mixture was refluxed for 5h then an additional portion of DDQ (19.3g, 85 mmol) was added. The mixture was then refluxed overnight, cooled and the deep red solution filtered. The solvent was then removed by rotary evaporation and the residual H₂O removed by azeotropic distillation with several portions of toluene. The

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material was dissolved in toluene (500 mL) and applied to a 40x10 cm column of SiO_2 and eluted with additional toluene as the solvent. The appropriate fractions were combined and the solvent removed to give 7.12g of crude material. This was crystallized twice from toluene, filtered and dried to give 5.35g of benzo[b]naphtho[2,3-d]thiophene-8-carbaldehyde, mp 182-185° (22.7% yield) which analyzed correctly (C,H,S) for the assigned structure.

8B 2-[(Benzo[b]naphtho[2,3-d]thiophen-8-ylmethyl)amino]-2-methyl-1,3-propanediol methanesulfonate 6/10 hydrate

Using procedure outlined in example 1, benzo[b]naphtho[2,3-d]thiophene-8-carbaldehyde (8A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-[(benzo[b]naphtho[2,3-d]thiophen-8-yl methyl)amino]-2-methyl-1,3-propanediol methanesulfonate 6/10 hydrate, mp 245-246° (dec) in 60.1% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 9

2-[(Benzo[b]naphtho[2,3-d]thiophen-7-ylmethyl)amino]-2-methyl-1,3-propanediol

9A Benzo[b]naphtho[2,3-d]thiophene-7-carbaldehyde

Using the procedure described in example 8, 7-methylbenzo[b]naphtho[2,3-d]thiophene (Cambridge Chemicals, Inc.) gave benzo[b]naphtho[2,3-d]thiophene-7-carbaldehyde, mp 199-200° in 18.7% yield which analyzed correctly for the assigned structure.

9B 2-[(Benzo[b]naphtho[2,3-d]thiophen-7-ylmethyl)amino]-2-methyl-1,3-propanediol methanesulfonate 1/2 hydrate

Using the procedure outlined in example 1, benzo[b]naphtho[2,3-d]thiophene-7-carbaldehyde (9A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-[(benzo[b]naphtho[2,3-d]thiophen-7-ylmethyl)amino]-2-methyl-1,3-propanediol methanesulfonate 1/2 hydrate, mp 210-211° (dec) in 75.8% yield which analyzed correctly (C,H,N,S) for the assigned structure

EXAMPLE 102-[(Benzo[b]naphtho[2,3-d]furan-11-ylmethyl)amino]-2-methyl-1,3-propanediol
methanesulfonate

Using the procedure outlined in example 1, benzo[b]naphtho[2,3-d]furan-11-carbaldehyde (2B) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-[(benzo[b]naphtho[2,3-d]furan-11-ylmethyl)-amino]-2-methyl-1,3-propanediol methanesulfonate, mp 219-220° (dec) in 68.8% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 112-[(5-Ethyl-5H-benzo[b]carbazol-7-yl)methylamino]-2-methyl-1,3-propanediol11A 5-Ethyl-5H-benzo[b]carbazole-7-carbaldehyde

Using the procedure outlined in example 8A, 5-ethyl-7-methyl-5H-benzo[b]carbazole (Cambridge Chemicals, Inc.) gave 5-ethyl-5H-benzo[b]carbazole-7-carbaldehyde, mp 130-133° in 15.4% yield which analyzed correctly (C,H,N) for the assigned structure.

11B 2-[(5-Ethyl-5H-benzo[b]carbazol-7-yl)methylamino]-2-methyl-1,3-propanediol
methanesulfonate

Using the procedure outlined in example 1, 5-ethyl-5H-benzo[b]carbazole-7-carbaldehyde (11A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-[(5-ethyl-5H-benzo[b]carbazol-7-yl)-methy]amino]-2-methyl-1,3-propanediol methanesulfonate, mp 219-220° (dec) in 40.2% yield which analyzed correctly (C,H,N,S) for the assigned structure.

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EXAMPLE 122-[(5-Ethyl-5H-benzo[b]carbazol-6-yl)methylamino]-2-methyl-1,3-propanediol12A 5-Ethyl-5H-benzo[b]carbazole-6-carbaldehyde

Using the procedure outlined in example 2, 5-ethyl-6-methyl-5H-benzo[b]carbazole (Cambridge Chemicals, Inc.) gave 5-ethyl-5H-benzo[b]carbazole-6-carbaldehyde, mp 95.5-96.5° in 44.9% yield which analyzed correctly (C,H,N) for the assigned structure.

12B 2-[(5-Ethyl-5H-benzo[b]carbazol-6-yl)methylamino]-2-methyl-1,3-propanediol methanesulfonate

Using the procedure outlined in example 1, 5-ethyl-5H-benzo[b]carbazole-6-carbaldehyde (12A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-[(5-ethyl-5H-benzo[b]carbazol-6-yl)methylamino]-2-methyl-1,3-propanediol methanesulfonate, mp 174-175° in 68.0% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 132-[(Benzo[b]naphtho[1,2-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol13A Benzo[b]naphtho[1,2-d]thiophen-5-carbaldehyde

Using the procedure outlined in example 2, benzo[b]naphtho[1,2-d]thiophene (H.G. Pars Pharmaceutical Laboratories, Inc.) gave benzo[b]naphtho[1,2-d]thiophen-5-carbaldehyde, mp 142-144° in 43.3% yield which analyzed correctly (C,H,S) for the assigned structure.

13B 2-[(Benzo[b]naphtho[1,2-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol methanesulfonate 1/2 hydrate

Using the procedure outlined in example 1, benzo[b]naphtho[1,2-d]thiophen-5-carbaldehyde (13A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-[(benzo[b]naphtho[1,2-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol methanesulfonate 1/2 hydrate, mp 209-209.5° in 73.7% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 142-Methyl-2-[(phenanthro[1,2-b]furan-2-ylmethyl)-amino]-1,3-propanediol14A Phenanthro[1,2-b]furan-2-methanol

To a round bottom flask equipped with magnetic stirring bar, reflux condenser, nitrogen inlet tube and bubbler was added ethyl phenanthro[1,2-b]furan-2-carboxylate (H.G. Pars Pharmaceutical Laboratories, Inc., 7.9g, 27.2 mmol), lithium borohydride (Aldrich, 0.65g, 30 mmol) and dry THF (400 mL). The mixture was stirred at reflux for 6h and then poured into H₂O (1L). The reaction mixture was acidified with 1N HCl and the resulting white solid was filtered, washed with additional H₂O (500 mL) then dissolved in CH₂Cl₂ (500 mL), dried (Na₂SO₄), filtered, concentrated to 200 mL and diluted to 500 mL with hexane. The resulting material was filtered, washed with hexane (100 mL) and placed in a vacuum oven overnight. A total of 6.1g of phenanthro[1,2-b]furan-2-methanol, mp 125-126° was obtained which analyzed correctly (C,H) for the assigned structure.

14B Phenanthro[1,2-b]furan-2-carbaldehyde

To a round bottom flask equipped with magnetic stirring bar, reflux condenser, nitrogen inlet tube and bubbler was added phenanthro[1,2-b]furan-2-methanol (14A, 5.84g, 23.5 mmol), barium manganate (Aldrich, 12.06g, 47 mmol) and dry CH₂Cl₂ (400 mL). The mixture was refluxed for 6h, filtered and the resulting dark yellow solution filtered through a small plug of silica gel to remove inorganic salts and baseline material. The solvent was then removed by rotary evaporation and the crude material recrystallized using CH₂Cl₂/ hexane to give after drying 5.27g (91% yield) of phenanthro[1,2-b]furan-2-carbaldehyde, mp 169° which analyzed correctly (C,H) for the assigned structure.

14C 2-Methyl-2-[(phenanthro[1,2-b]furan-2-ylmethyl)amino]-1,3-propanediol
methanesulfonate 1/2 hydrate

Using the procedure outlined in example 1, phenanthro[1,2-b]furan-2-carbaldehyde (14B) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-

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methyl-2-[(phenanthro[1,2-b]furan-2-ylmethyl)amino]-1,3-propanediol methanesulfonate 1/2 hydrate, mp 168-170° (dec) in 57.1% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 15

2-Methyl-2-[(phenanthro[1,2-b]furan-11-ylmethyl)amino]-1,3-propanediol

15A Ethyl 11-formyl-phenanthro[1,2-b]furan-2-carboxylate

Using the procedure outlined in example 2B, ethyl phenanthro[1,2-b]furan-2-carboxylate (H.G.Pars Pharmaceutical Laboratories, Inc.) gave a crude mixture of aldehydes in 54% yield which was used in the next step without purification. An analytical sample of the main component of this mixture, ethyl 11-formyl-phenanthro[1,2-b]furan-2-carboxylate mp *** was produced by column chromatography followed by crystallization (CH₂Cl₂/hexane).

15B Phenanthro[1,2-b]furan-11-carbaldehyde

To a round bottom flask equipped with magnetic stirring bar, condenser, and nitrogen inlet tube and bubbler was added ethyl 11-formyl-phenanthro[1,2-b]furan-2-carboxylate (15A, 2.5g, 7.8 mmol), 1N sodium hydroxide solution (25 mL), THF (50 mL) and H₂O (25 mL). The mixture was refluxed for 2h until the reaction was homogeneous. The mixture was acidified with 1N HCl and the solvent removed by rotary evaporation. The crude solid was then heated to 150° with copper powder (0.9g) and quinoline (Aldrich, 25 mL) for 1h. The reaction mixture was cooled and the quinoline removed under vacuum to give a crude dark green solid. After chromatography and crystallization (CH₂Cl₂/ hexane) 0.71g (37% yield) of phenanthro[1,2-b]furan-11-carbaldehyde, mp 145-150° was obtained which analyzed correctly (C,H) for the assigned structure.

15C 2-Methyl-2-[(phenanthro[1,2-b]furan-4-ylmethyl)amino]-1,3-propanediol methanesulfonate

Using the procedure outlined in example 1, phenanthro[1,2-b]furan-11-carbaldehyde (15B) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-

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methyl-2-[(phenanthro[1,2-b]furan-11-ylmethyl)-amino]-1,3-propanediol methanesulfonate, mp 186-188° (dec) in 57.6% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 16

2-Methyl-2-[(phenanthro[1,2-b]thiophen-2-ylmethyl)amino]-1,3-propanediol

16A Phenanthro[1,2-b]thiophen-2-methanol

Using the procedure outlined in 14A, ethyl phenanthro[1,2-b]thiophen-2-carboxylate (H.G. Pars Pharmaceutical Laboratories, Inc.) gave phenanthro[1,2-b]thiophen-2-methanol, mp 169-170.5° in 98.0% yield which analyzed correctly (C,H,S) for the assigned structure.

16B Phenanthro[1,2-b]thiophene-2-carbaldehyde

Using the procedure outlined in 14B, phenanthro[1,2-b]thiophene-2-methanol (16A) gave phenanthro[1,2-b]thiophene-2-carbaldehyde. mp 209-210° in 82.9% yield which analyzed correctly (C,H,S) for the assigned structure.

16C 2-Methyl-2-[(phenanthro[1,2-b]thiophen-2-ylmethyl)amino]-1,3-propanediol methanesulfonate 3/5 hydrate

Using the procedure outlined in example 1, phenanthro[1,2-b]thiophene-2-carbaldehyde (16B) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-methyl-2-[(phenanthro[1,2-b]thiophen-2-yl)methyl)amino]-1,3-propanediol methanesulfonate 3/5 hydrate, mp 209-209.5° (dec) in 82.7% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 17

2-Methyl-2-[(phenanthro[1,2-b]thiophen-11-ylmethyl)amino]-1,3-propanediol

17A Phenanthro[1,2-b]thiophene-11-carbaldehyde

Using the procedure outlined in example 2B, ethyl phenanthro[1,2-b]thiophene-2-carboxylate was formylated to give a low yield of a mixture of

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aldehyde esters. The mixture was directly hydrolyzed as in example 15B and the resulting crude mixture of aldehyde acids was decarboxylated as in example 15B to give a crude mixture of aldehydes. The main component of the mixture, phenanthro[1,2-b]-thiophene-11-carbaldehyde, mp 161.5-162.5° was obtained after chromatography and crystallization in 3.1% overall yield for the sequence and analyzed correctly (C,H,S) for the assigned structure.

17B 2-Methyl-2-[(phenanthro[1,2-b]thiophen-11-ylmethyl)amino]-1,3-propanediol methanesulfonate

Using the procedure outlined in example 1, phenanthro[1,2-b]-thiophene-11-carbaldehyde (17B) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-methyl-2-[(phenanthro[1,2-b]-thiophen-11-ylmethyl)amino]-1,3-propanediol methanesulfonate, mp 206-207° (dec) in 56.5% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 18

2-Methyl-2-[(phenanthro[4,3-b]furan-2-ylmethyl)amino]-1,3-propanediol

18A Phenanthro[4,3-b]furan-2-methanol

Using the procedure outlined in example 14A, ethyl phenanthro[4,3-b]furan-2-carboxylate (H.G. Pars Pharmaceutical Laboratories, Inc.) gave a 91% yield of phenanthro[4,3-b]furan-2-methanol, mp 125-126° which analyzed correctly for the assigned structure.

18B Phenanthro[4,3-b]furan-2-carbaldehyde

Using the procedure outlined in example 14B, phenanthro[4,3-b]furan-2-methanol (18A) gave a 91.2% yield of phenanthro[4,3-b]furan-2-carbaldehyde mp 169° which analyzed correctly for the assigned structure.

18C 2-Methyl-2-[(phenanthro[4,3-b]furan-2-ylmethyl)amino]-1,3-propanediol methanesulfonate

Using the procedure outlined in example 1, phenanthro[4,3-b]furan-2-carbaldehyde (18B) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-methyl-2-[(phenanthro[4,3-b]furan-2-ylmethyl)amino]-1,3-propanediol

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methanesulfonate, mp 186-188° (dec) in 56.5% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 19

2-Methyl-2-[(phenanthro[4,3-b]thiophen-7-ylmethyl)amino]-1,3-propanediol

19A Phenanthro[4,3-b]thiophene-7-carbaldehyde

Using the procedure outlined in example 17A ethyl phenanthro[4,3-b]thiophene-2-carboxylate (H.G.Pars Pharmaceutical Laboratories, Inc.) gave a 6.7% yield of phenanthro[4,3-b]thiophene-7-carbaldehyde mp 173-177° which analyzed correctly (C,H,S) for the assigned structure.

19B 2-Methyl-2-[(phenanthro[4,3-b]thiophen-7-ylmethyl)amino]-1,3-propanediol methanesulfonate 1/4 hydrate

Using the procedure outlined in example 1, phenanthro[4,3-b]thiophene-7-carbaldehyde (19A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-methyl-2-[(phenanthro[4,3-b]thiophen-7-ylmethyl)amino]-1,3-propanediol methanesulfonate 1/4 hydrate, mp 189-191° (dec) in 53.8% yield which analyzed correctly (C,H,N,S) for the assigned structure.

EXAMPLE 20

2-Methyl-2-[(phenanthro[9,10-b]furan-2-ylmethyl)amino]-1,3-propanediol

20A Using the procedure outlined in example 2, phenanthro[9,10-b]furan (prepared by the procedure of P.Muller and J. Pfyffer, *Chimia* **38**, 79 (1984)) gave, phenanthro[9,10-b]furan-2-carbaldehyde, mp 84-85° in 32.8% yield which analyzed correctly (C,H) for the assigned structure

20B 2-Methyl-2-[(phenanthro[9,10-b]furan-2-ylmethyl)amino]-1,3-propanediol methanesulfonate 1/5 hydrate 1/5 EtOH

Using the procedure outlined in example 1, phenanthro[9,10-b]furan-2-carbaldehyde (20A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-methyl-2-[(phenanthro[9,10-b]furan-2-ylmethyl)amino]-1,3-propanediol methanesulfonate 1/5 hydrate 1/5 EtOH, mp 218-219° (dec) in 39.2% yield which analyzed correctly (C,H,N,S) for the assigned structure.

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EXAMPLE 212-Methyl-2-[(phenanthro[9,10-c]thiophen-1-ylmethyl)-amino-1,3-propanediol21A Phenanthro[9,10-c]thiophene-1-carbaldehyde

Using the procedure outlined in example 2, phenanthro[9,10-c]-thiophene (H.G. Pars Pharmaceutical Laboratories, Inc.) gave phenanthro[9,10-c]thiophene-1-carbaldehyde, mp 198-199° in 85.9% yield which analyzed correctly (C,H,S) for the assigned structure.

21B 2-Methyl-2-[(phenanthro[9,10-c]thiophen-1-ylmethyl)amino]-1,3-propanediol methanesulfonate 1/4 hydrate

Using the procedure outlined in example 1, phenanthro[9,10-c]-thiophene-1-carbaldehyde (21A) and 2-amino-2-methyl-1,3-propanediol (Aldrich) gave 2-methyl-2-[(phenanthro[9,10-c]thiophen-1-ylmethyl)amino]-1,3-propanediol methanesulfonate 1/4 hydrate, mp 180-187° (dec) in 39.2% yield which analyzed correctly (C,H,N,S) for the assigned structure.

Antitumor Screening Results

Methods for evaluating the antitumor activity of these compounds are essentially those used in the Tumor Panel by the Development Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, A. Goldin, et al., Methods in Cancer Research, Vol. XVI, p. 165, Academic Press (1979). Some modifications, in dose level and schedule have been made to increase the testing efficiency.

Lymphocytic Leukemia P388/0 Test

CD2-F₁ mice, of the same sex weighing within 20±3g, are used for this test. Control and test animals are injected intraperitoneally with a suspension of 10⁶ viable P388/0 tumor cells on day 0. In each test several dose levels which bracket the LD₂₀ for the compound are evaluated; each dose level group contains 6 animals. The test compounds are prepared either in physiologic saline containing 0.05% Tween 80 or distilled water containing 5% dextrose and are administered intraperitoneally on days, 1, 5, and 9 relative to tumor implant. Doses are on a mg/kg basis according to individual animals' body weights. the day of death for each animal is recorded, the median identified for each group

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and the ratios of median survival time for treated (T)/control (C) groups are calculated. The criterion for activity is $T/C \times 100 \geq 120\%$. Results of P388/0 testing are summarized in Table I below.

TABLE I

<u>Compound of Formula</u>	<u>Optimal Dose (mg/kg)</u>	<u>T/C x 100% (Excluding 30 Day Survivors)</u>	<u>LD₂₀ mg/Kg</u>	<u>30 DAY Survivors</u>
1	65	+210	35	1/6
2B	100	+204	125	1/6
3B	20	+230	10	2/6
4C	80	no deaths	55	6/6
5B	125	+255	100	4/6
6B	55	+210	35	0/6

Formulation Examples

A. TABLET

Compound of Formula I (as methanesulphonate)	500.0. mg
Pregelatinised Corn Starch	60.0 mg
Sodium Starch Glycolate	36.0 mg
Magnesium Stearate	4.0 mg

The Compound of formula (I) is finely ground and intimately mixed with the powdered excipients, pregelatinised corn starch and sodium starch glycolate. The powders are wetted with purified water to form granules. The granules are dried and mixed with the magnesium stearate. The formulation is then compressed into tablets weighing approximately 600 mg each.

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B. TABLET

Compound of formula (I)	500.0 mg
Corn Starch	70.0 mg
Lactose	83.8 mg
Magnesium Stearate	4.2 mg
Polyvinylpyrrolidone	14.0 mg
Stearic Acid	28.0 mg

The Compound of formula (I) is finely ground and intimately mixed with the powdered excipients, corn starch and lactose. The powders are wetted with a solution of polyvinylpyrrolidone dissolved in purified water and denatured alcohol to form granules. The granules are dried and mixed with the powdered stearic acid and magnesium stearate. The formulation is then compressed into tablets weighing approximately 700 mg each.

C. CAPSULES

Compound of formula (I)	500.0 mg
Corn Starch	50.0 mg
Magnesium Stearate	3.0 mg

The finely divided compound of formula (I) is mixed with powdered corn starch and wetted with denatured alcohol to densify the powder. The dried powder is mixed with stearic acid and filled into hard-shell gelatin capsules.

D. SYRUP

Compound of formula (I)	250.0 mg
Ethanol	250.0 mg
Glycerin	500.0 mg
Sucrose	3,500.0 mg
Flavouring Agent	q.s.
Colouring Agent	q.s.
Preserving Agent	0.1%
Purified Water	q.s. to 5.0 ml

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The Compound of formula (I) is dissolved in the ethanol, glycerin, and a portion of the purified water. The sucrose and preserving agent are dissolved in another portion of hot purified water, and then the colouring agent is added and dissolved. The two solution are mixed and cooled before the flavouring agent is added. Purified water is added to final volume. The resulting syrup is thoroughly mixed.

E. IV INJECTION

Compound of formula (I) (as methanesulphonate)	5.0 mg
Glycerin	q.s. for isotonicity
Preservative	0.1%
Hydrochloric Acid or	as needed for
Sodium Hydroxide	pH adjustment
Water for Injection	q.s. to 1 ml

The compound of formula (I) and preservative is added to the glycerin and a portion of the water for injection. The pH is adjusted with hydrochloric acid or sodium hydroxide. Water for injection is added to final volume and solution is complete after thorough mixing. The solution is sterilised by filtration through a 0.22 micrometer membrane filter and aseptically filled into sterile 10 ml ampoules or vials.

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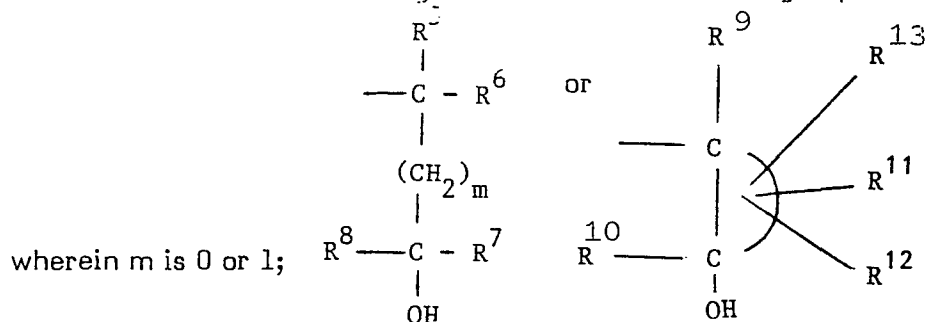
1. A compound of the formula (I):



or a monomethyl or monoethyl ether thereof, the compound of formula (I) including the said ethers containing no more than 29 carbon atoms in total; an ester thereof; a salt thereof;

wherein Ar is a 6,6,6,5 tetracyclic aromatic ring system having 15 to 17 ring atoms, the five membered ring containing one heteroatom, optionally substituted by one or two substituents, said substituents containing not more than four carbon atoms in total when taken together and being the same or different and are selected from halogen; cyano; C₁₋₄ alkyl or C₁₋₄ alkoxy, each optionally substituted by hydroxy or C₁₋₂ alkoxy; halogen substituted C₁₋₂ alkyl or C₁₋₂ alkoxy; a group S(O)_nR² wherein n is an integer 0,1 or 2 and R² is C₁₋₂ alkyl optionally substituted by hydroxy or C₁₋₂ alkoxy; or Ar is optionally substituted by a group NR³R⁴ containing not more than 5 carbon atoms wherein R³ and R⁴ are the same or different and each is a C₁₋₃ alkyl group or NR³R⁴ forms a five- or six-membered heterocyclic ring optionally containing one or two additional heteroatoms;

R¹ contains not more than eight carbon atoms and is a group



R⁵ and R⁶ are the same or different and each is hydrogen or C₁₋₅ alkyl optionally substituted by hydroxy;

R⁷ and R⁸ are the same or different and each is hydrogen or C₁₋₃ alkyl; -C-C is a five- or six-membered saturated carbocyclic ring;

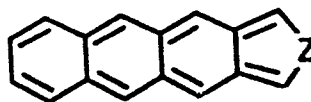
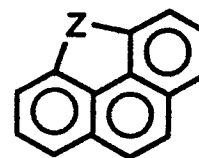
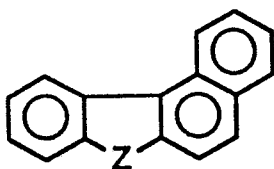
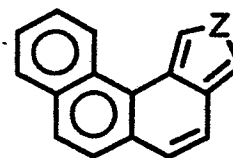
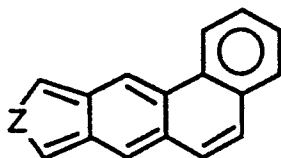
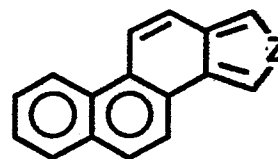
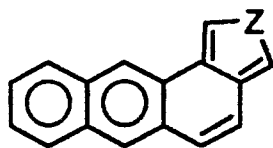
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R^9 is hydrogen, methyl or hydroxymethyl;

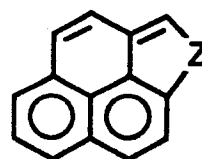
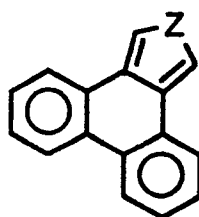
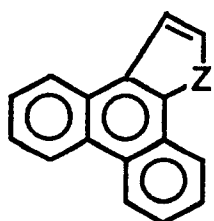
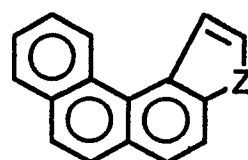
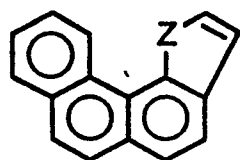
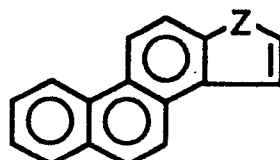
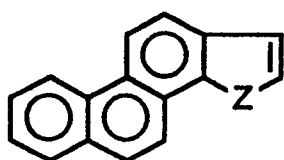
R^{10} , R^{11} and R^{12} are the same or different and each is hydrogen or methyl;

R^{13} is hydrogen, methyl, hydroxy, or hydroxymethyl.

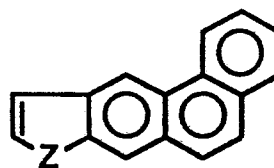
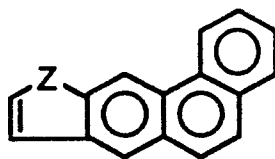
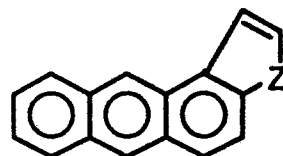
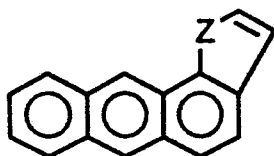
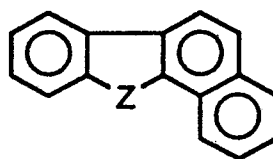
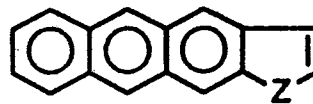
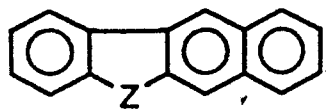
2. A compound according to claim 1 wherein the tetracyclic aromatic ring system is chosen from the group comprising:



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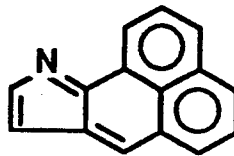
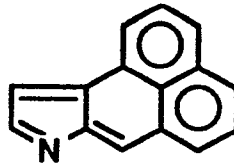
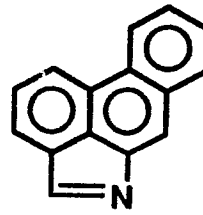
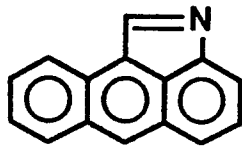
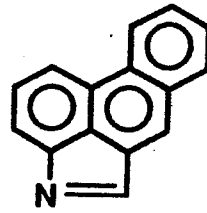
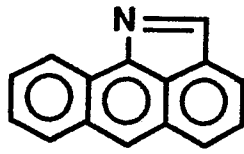


Z is a heteroatom

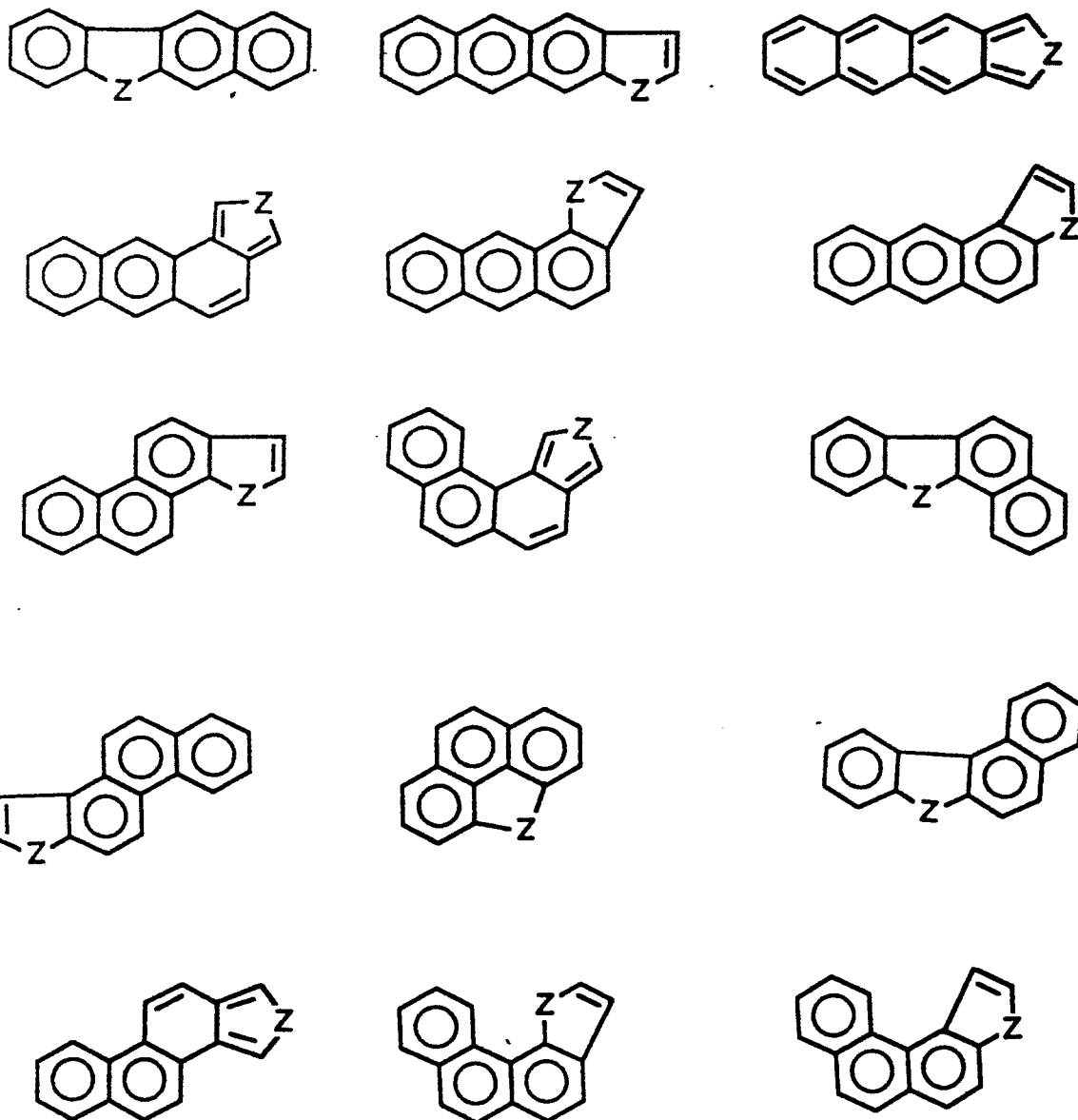


Z is a heteroatom

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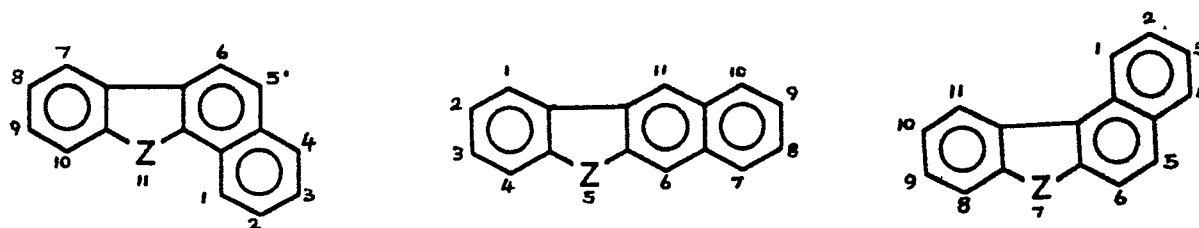
3. A compound according to claim 1 wherein Ar is selected from one of the following ring systems:



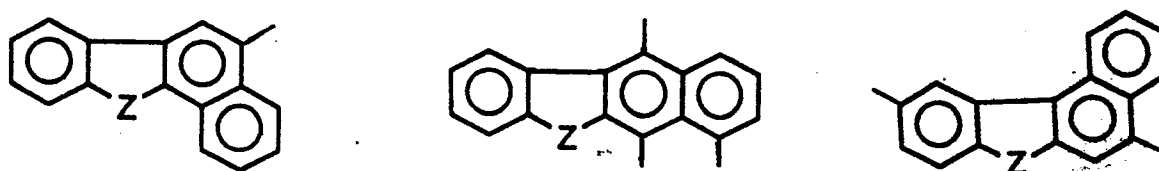
wherein Z is a heteroatom.

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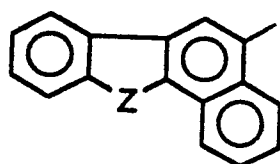
4. A compound according to claim 3 wherein Ar is selected from:



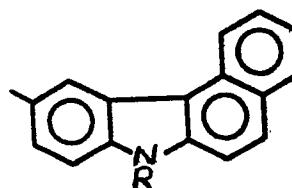
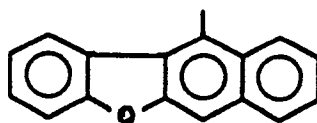
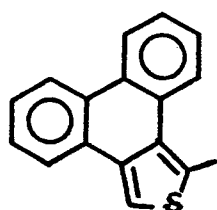
5. A compound according to claim 4 wherein the CH_2NHR^1 side chain is attached at one of the positions indicated below:



6. A compound according to claim 1 wherein Ar is selected from the group comprising:

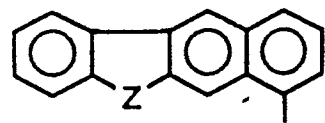
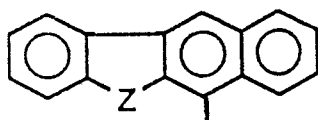


wherein Z = O, S,
NMe or NEt



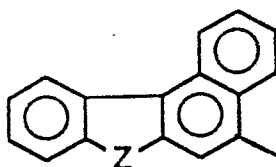
wherein R=Me or Et

or



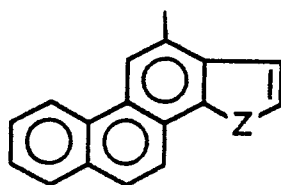
wherein Z= S or O

and



wherein Z= S,O,
NMe, or NEt.

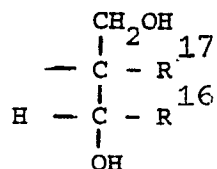
7. A compound of the formula (I) according to claim 1 in which Ar is:



wherein Z= S,O,
NMe, or NEt.

8. A compound according to claim 1 wherein Ar is 7H-benzo[c]carbazol-10-yl or benzo[b]naphtho[2,1-d]furan-5-yl.

9. A compound according to claim 1 wherein R¹ is



wherein R¹⁶ is hydrogen or methyl and R¹⁷ is hydrogen, methyl or ethyl.

10. 2-[(9-Benzo[b]naphtho[2,1-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[(Benzo[b]naphtho[2,3-d]furan-6-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[(Benzo[b]naphtho[1,2-d]furan-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[(Benzo[b]naphtho[2,1-d]furan-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-Methyl-2-[(7-methyl-7H-benzo[c]carbazol-10-yl)methyl]amino]-1,3-propanediol
 2-[(Benzo[b]naphtho[2,3-d]thiophen-6-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-(5-Ethyl-(benzo[b]carbazol-7-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-(Benzo[b]naphtho[2,3-d]furan-11-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-(Benzo[b]naphtho[2,3-d]thiophen-8-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-[(5-Ethyl)-benzo[b]carbazol-6-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-[(Benzo[b]naphtho[2,3-d]thiophen-7-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-[(Phenanthro[9,10-c]thiophen-1-ylmethyl)amino)-2-methyl-1,3-propanediol
 2-Methyl-2-[(phenanthro[9,10-b]furan-2-ylmethyl)amino]-1,3-propanediol
 2-[(Benzo[b]naphtho[1,2-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-Methyl-2-[(phenanthro[4,3-b]furan-2-ylmethyl)amino]-1,3-propanediol
 2-[(Phenanthro[1,2-b]thiophen-2-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-Methyl-2-[(phenanthro[1,2-b]furan-2-ylmethyl)amino]-1,3-propanediol
 2-Methyl-2-[(phenanthro[4,3-b]thiophen-7-ylmethyl)amino]-1,3-propanediol
 2-[(Phenanthro[1,2-b]thiophen-4-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[(Phenanthro[1,2-b]furan-4-ylmethyl)amino]-2-methyl-1,3-propanediol
 2-[Benzo[b]naphtho[2,3-d]furan-7-ylmethyl)amino]-2-methyl-1,3-propanediol
 and monomethyl ethers, monoethyl ethers, esters and acid addition salts thereof.
11. A pharmaceutical formulation comprising a compound as defined in any of claims 1 to 10, and a pharmaceutically acceptable carrier therefor.

12. A process for the preparation of a compound of the formula (I), as defined in claim 1, which process comprises:
- (a) the reduction of a compound Ar CH=NR^1 or an appropriately protected derivative thereof, followed by deprotection where appropriate;
 - (b) the reduction of a compound Ar.CO.NHR^1 , wherein the hydroxy groups are optionally protected, followed by deprotection of the hydroxy groups where appropriate;
 - (c) the reaction of a compound $\text{Ar CH}_2\text{L}$, wherein L is a leaving group, with a compound NH_2R^1 ;
 - (d) any other method known in the art for the preparation of analogous compounds.
13. Novel chemical intermediates of the formulae Ar CH=NR^1 , Ar.CO.NHR^1 and $\text{Ar CH}_2\text{L}$ wherein Ar and R^1 are as defined in claim 1 and L is a leaving group.

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14. A compound of the formula (I) or an ether, ester or acid addition salt thereof, as defined in claim 1, for use in the treatment of tumours.
15. A compound of the formula (I) or an ether, ester or acid addition salt thereof, as defined in claim 1, for use in the preparation of a medicament for the treatment of tumours.

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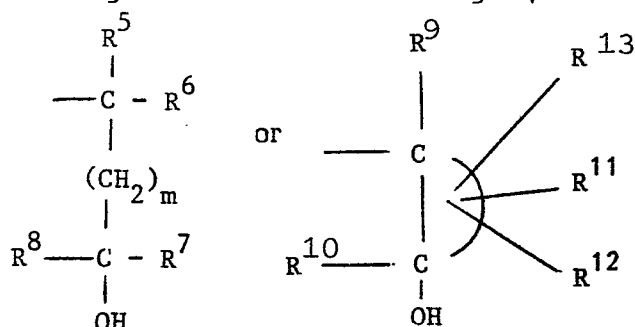
1. A process for the preparation of a compound of the formula (I):



or a monomethyl or monoethyl ether thereof, the compound of formula (I) including the said ethers containing no more than 29 carbon atoms in total; an ester thereof; a salt thereof;

wherein Ar is a 6,6,6,5 tetracyclic aromatic ring system having 15 to 17 ring atoms, the five membered ring containing one heteroatom, optionally substituted by one or two substituents, said substituents containing not more than four carbon atoms in total when taken together and being the same or different and are selected from halogen; cyano; C_{1-4} alkyl or C_{1-4} alkoxy, each optionally substituted by hydroxy or C_{1-2} alkoxy; halogen substituted C_{1-2} alkyl or C_{1-2} alkoxy; a group $\text{S(O)}_n \text{R}^2$ wherein n is an integer 0, 1 or 2 and R^2 is C_{1-2} alkyl optionally substituted by hydroxy or C_{1-2} alkoxy; or Ar is optionally substituted by a group $\text{NR}^3 \text{R}^4$ containing not more than 5 carbon atoms wherein R^3 and R^4 are the same or different and each is a C_{1-3} alkyl group or $\text{NR}^3 \text{R}^4$ forms a five- or six-membered heterocyclic ring optionally containing one or two additional heteroatoms;

R^1 contains not more than eight carbon atoms and is a group



wherein m is 0 or 1;

R^5 and R^6 are the same or different and each is hydrogen or C_{1-5} alkyl optionally substituted by hydroxy;

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R^7 and R^8 are the same or different and each is hydrogen or C_{1-3} alkyl; -
C-C is a five-or-six-membered saturated carbocyclic ring;

R^9 is hydrogen, methyl or hydroxymethyl;

R^{10} , R^{11} and R^{12} are the same or different and each is hydrogen or methyl;

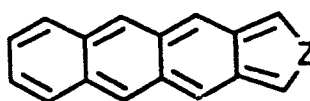
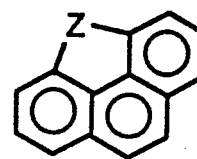
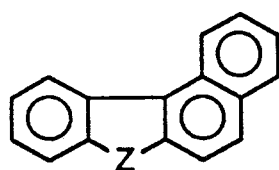
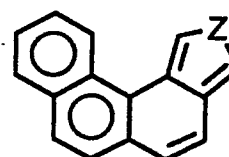
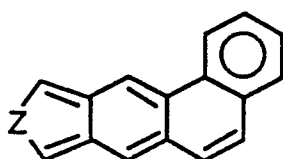
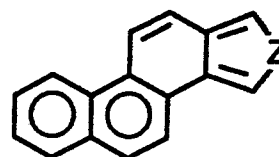
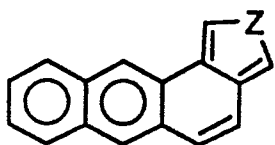
R^{13} , is hydrogen, methyl, hydroxy, or hydroxymethyl;

which process comprises:

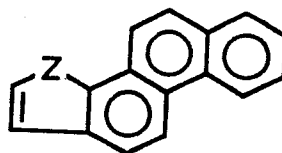
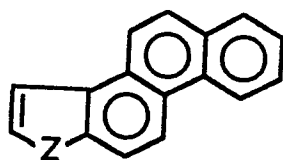
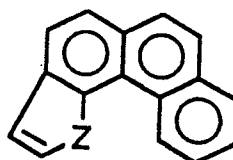
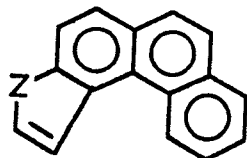
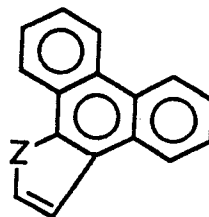
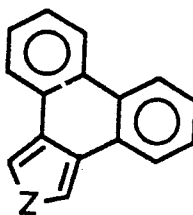
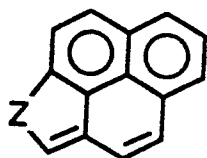
- (a) the reduction of a compound $ArCH=NR$; or an appropriately protected derivative thereof, followed by deprotection where appropriate;
- (b) the reduction of a compound $Ar.CO.NHR^1$, wherein the hydroxy groups are optionally protected, followed by deprotection of the hydroxy groups where appropriate;
- (c) the reaction of a compound $ArCH_2L$, wherein L is a leaving group, with a compound NH_2R^1 ;
- (d) any method known in the art for the preparation of analogous compounds.

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2. A process according to claim 1 for the preparation of a compound wherein the aromatic ring system is selected from the group comprising:

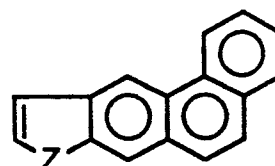
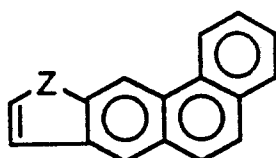
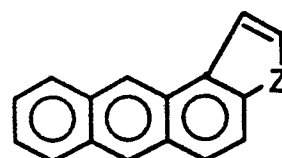
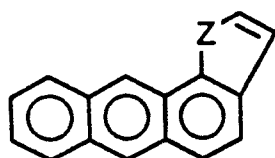
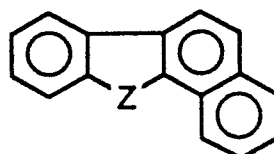
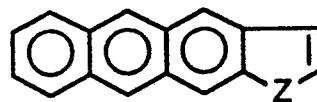
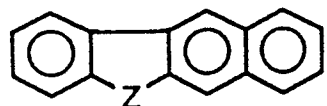


Z is a heteroatom



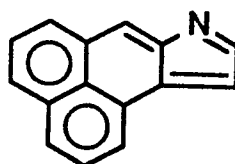
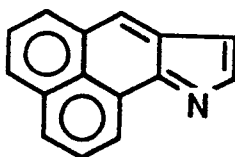
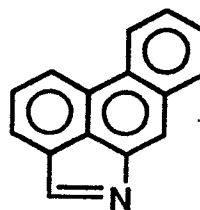
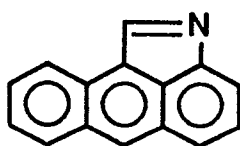
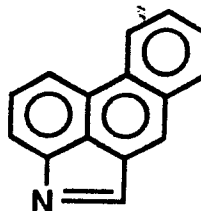
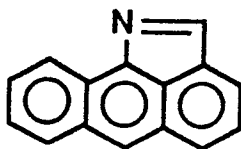
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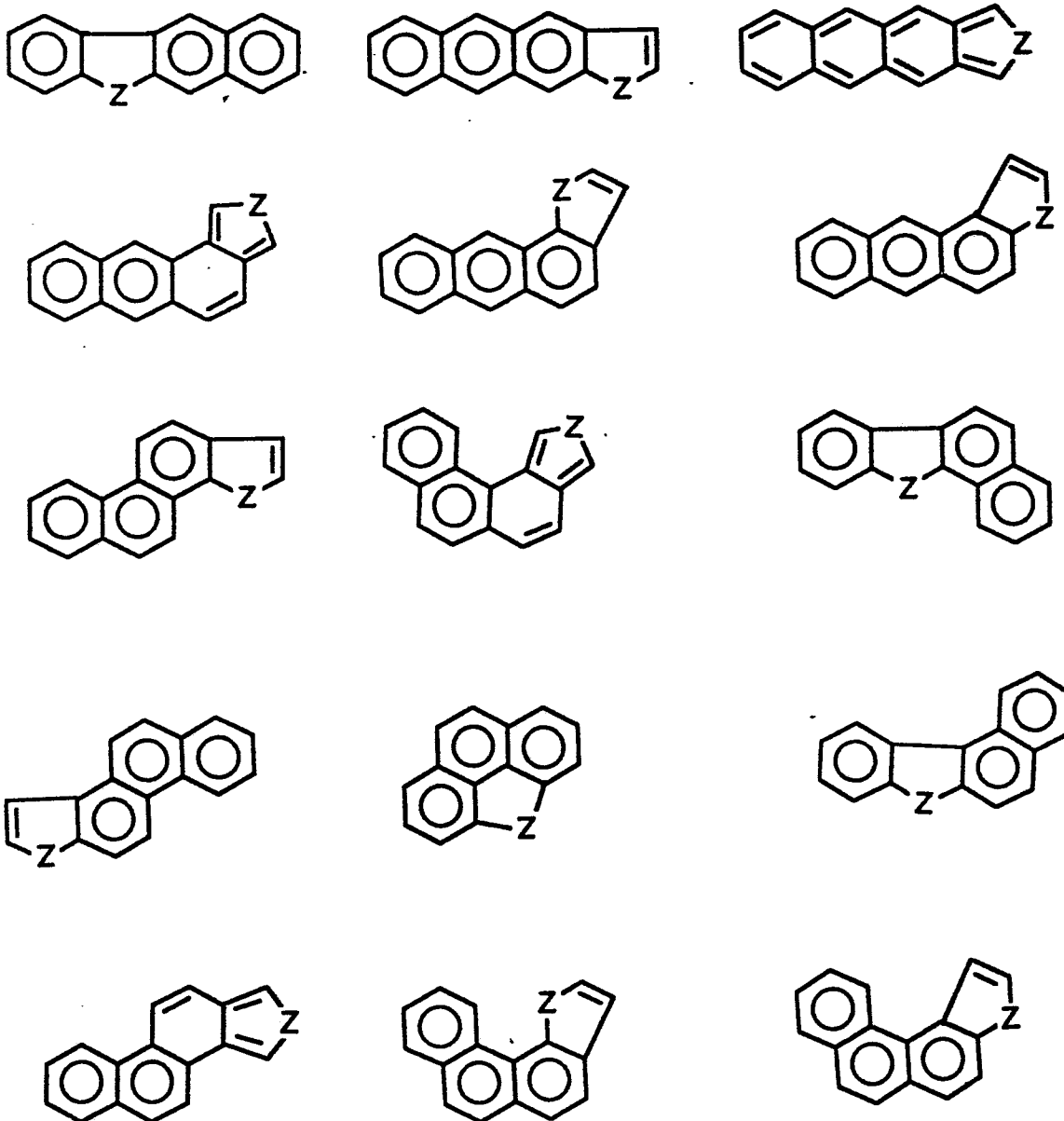
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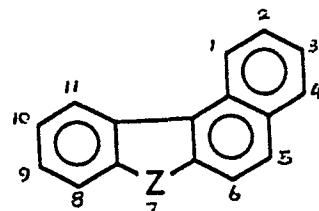
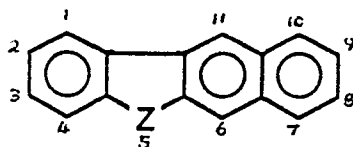
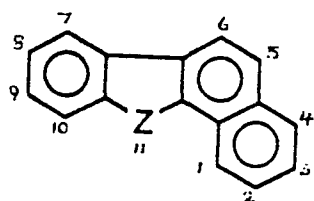
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3. A process according to claim 1 for the preparation of a compound wherein Ar is selected from one of the following ring systems:

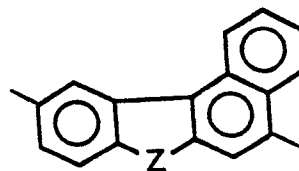
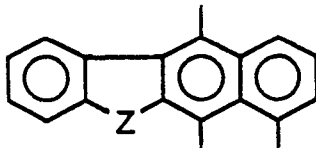
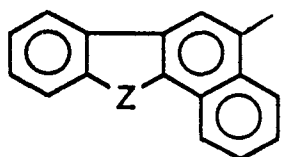


wherein Z is a heteroatom.

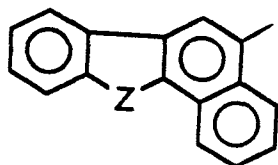
4. A process to claim 1 for preparing a compound of the formula (I) wherein Ar is selected from:



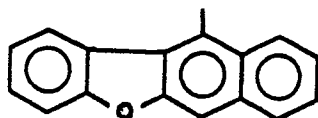
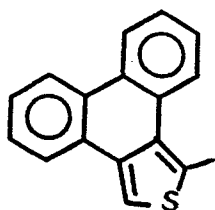
5. A process according to claim 4 for preparing a compound wherein the CH_2NHR^1 side chain is attached at one of the positions indicated below:



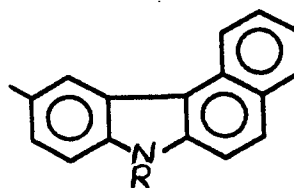
6. A process according to claim 1 for preparing a compound of the formula (I) wherein Ar is selected from:



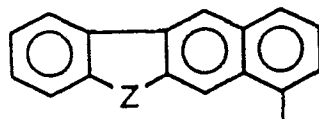
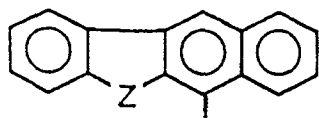
wherein Z = O, S,
NMe or NEt



or

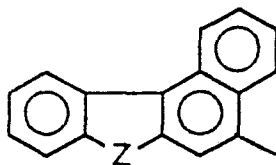


where R=Me or Et



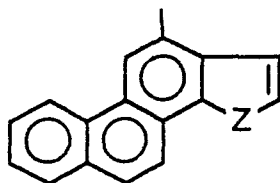
wherein Z = S or O

and



wherein Z = S, O
NMe or NEt

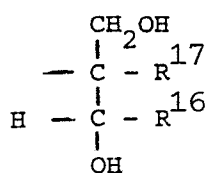
7. A process according to claim 1 for preparing a compound of the formula (I) wherein Ar is:



wherein Z = S, O, NMe or NEt

8. A process according to claim 1 for preparing a compound of the formula (I) wherein Ar is 7H-benzo[c]carbazol-10-yl or benzo[b]naphtho[2,1-d]furan-5-yl.

9. A process according to claim 1 for preparing a compound of the formula (I) wherein R¹ is



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wherein R^{16} is hydrogen or methyl and R^{17} is hydrogen, methyl or ethyl.

10. A process according to claim 1 for preparing a compound selected from:
 - 2-[(9-Benzo[b]naphtho[2,1-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-[(Benzo[b]naphtho[2,3-d]furan-6-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-[(Benzo[b]naphtho[1,2-d]furan-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-[(Benzo[b]naphtho[2,1-d]furan-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-Methyl-2-[(7-methyl-7H-benzo[c]carbazol-10-yl)methyl]amino]-1,3-propanediol
 - 2-[(Benzo[b]naphtho[2,3-d]thiophen-6-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-(5-Ethyl-(benzo[b]carbazol-7-ylmethyl)amino)-2-methyl-1,3-propanediol
 - 2-(Benzo[b]naphtho[2,3-d]furan-11-ylmethyl)amino)-2-methyl-1,3-propanediol
 - 2-(Benzo[b]naphtho[2,3-d]thiophen-8-ylmethyl)amino)-2-methyl-1,3-propanediol
 - 2-[(5-Ethyl)-benzo[b]carbazol-6-ylmethyl)amino)-2-methyl-1,3-propanediol
 - 2-[(Benzo[b]naphtho[2,3-d]thiophen-7-ylmethyl)amino)-2-methyl-1,3-propanediol
 - 2-[(Phenanthro[9,10-c]thiophen-1-ylmethyl)amino)-2-methyl-1,3-propanediol
 - 2-Methyl-2-[(phenanthro[9,10-b]furan-2-ylmethyl)amino]-1,3-propanediol
 - 2-[(Benzo[b]naphtho[1,2-d]thiophen-5-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-Methyl-2-[(phenanthro[4,3-b]furan-2-ylmethyl)amino]-1,3-propanediol
 - 2-[(Phenanthro[1,2-b]thiophen-2-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-Methyl-2-[(phenanthro[1,2-b]furan-2-ylmethyl)amino]-1,3-propanediol
 - 2-Methyl-2-[(phenanthro[4,3-b]thiophen-7-ylmethyl)amino]-1,3-propanediol
 - 2-[(Phenanthro[1,2-b]thiophen-4-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-[(Phenanthro[1,2-b]furan-4-ylmethyl)amino]-2-methyl-1,3-propanediol
 - 2-[Benzo[b]naphtho[2,3-d]furan-7-ylmethyl)amino]-2-methyl-1,3-propanediol
 and monomethyl ethers, monoethyl ethers, esters and acid addition salts thereof.
11. Novel chemical intermediates of the formulae $ArCH=NR^1$, $Ar.CO.NHR^1$ and $ArCH_2L$ as defined in claim 1.
12. A pharmaceutical formulation comprising a compound of the formula (I), or an ether, ester or acid addition salt thereof, as defined in claim 1, and a pharmaceutically acceptable carrier therefor.